

CASE REPORT

Vernal shield ulcers treated with frequently installed topical cyclosporine 0.05% eyedrops

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Abstract

Purpose To report on the beneficial results of an intense regimen of 0.05% cyclosporine eye drops, eight times a day in patients with therapy resistant vernal shield ulcers.

Methods Case cohort of four eyes of three male children with vernal keratoconjunctivitis complicated by shield ulcers, who were treated with frequent cyclosporine 0.05% eye drops and observed for up to 5 years.

Results Quick resolution of the shield ulcers and complete re-epithelialization within 14–25 days was observed after adding intensive treatment with cyclosporine 0.05% to regular anti-inflammatory, histamine

blocking, and surgical therapy. In one patient, additional scraping of the bottom of the ulcer was needed. **Conclusions** In patients with vernal shield ulcers, frequent installation of low-concentration cyclosporine eye drops seems to have a promising therapeutical value.

Keywords Vernal keratoconjunctivitis · Shield ulcer · Cyclosporine A · Immunomodulation · Vernal catarrh · Allergy

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, seasonal, inflammatory ocular surface disease affecting mostly children and young adults. It occurs more frequently in males with an atopic background and predominantly in warm climates. Severe visual impairment can result if the cornea is involved. Corneal shield ulcers form as punctate epithelial erosions coalesce into a defect. Slow healing leads to corneal scarring, opacity, surface irregularity, and astigmatism. Shield ulcers occur in 3–11% of patients with VKC [1].

There is no consensus as to the best topical management of the corneal involvement in VKC. Currently, steroids, mast cell inhibitors, artificial tears, antibiotics, bandage soft contact lenses, and cryotherapy or surgical excision of papillae are the mainstay of

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treatment. However, ulcers are commonly refractory to these treatment modalities. In addition, these therapies may cause ocular complications including cataract, increased intraocular pressure, and secondary infection. If treatment succeeds re-epithelialization can take up to several months [2]. When shield ulcers are treated inadequately, secondary infections might occur due to the characteristic persistent epithelial defect [3, 4].

Topical cyclosporine (CsA) has been advocated as an effective and safe treatment for VKC [5, 6]. The topical CsA treatment for shield ulcer subgroup of patients has so far not been thoroughly studied. Cetinkaya et al. [7] presented four patients with shield ulcers treated with topical oil solution of 2% CsA four times a day and observed a recurrence of corneal defects in three cases when the concentration was reduced to 0.05% CsA four times a day. However, higher concentrations of CsA may cause more irritation [6], which may potentially lead to non-compliance. A lower concentration solution, instilled more frequently, might be an option that increases the available active CsA while reducing the chance of treatment failure from non-compliance secondary to local irritation. Also lower concentrations are effective in vitro, while higher concentrations are shown to slow down epithelial regrowth [8]. Until now, only Kumar et al reported a case of intensive (eight times a day) regimen with 0.05% CsA combined with conventional topical therapy for shield ulcer [9]. Caputo et al. reported on successful combined treatment with surgical debridement and topical CsA; however, higher concentrations of CsA 1% were used [10].

We present the outcomes of three patients with corneal shield ulcers in VKC managed with combined therapy of intensive topical CsA 0.05% in addition to corticosteroids and anti-histamines/mast cell stabilizers with artificial tears.

Materials and methods

This is a retrospective case series. Patients disease severity was graded using the Clinical Classification Table (Table 1) as described by Lapid-Gortzak et al. [11]. For the classification of the shield ulcers, we used the Shield Ulcer and/or Plaque Development Table as described by Cameron [2]: Transparent ulcers grade 1,

opacified ulcers grade 2, and elevated ulcers grade 3. The study was deemed exempt from full review by the medical ethical committee of the Academic Medical Center, University of Amsterdam, because of the retrospective nature and deidentified patient data used.

Patient 1

An 11-year-old boy with asthma and atopy was referred with an ulcer on the right cornea. On examination, visual acuity (VA) was 0.05 (Snellen). Slit lamp examination revealed conjunctival hyperemia, with giant papillae and copious mucus upon eversion of both upper eyelids (Fig. 1). A corneal epithelial defect of 1.7×2.5 mm was noted, and Horner-Trantas dots were seen at the limbus. The diagnosis severe VKC with shield ulcer (grade 1) was made. The patient was treated with topical prednisone 1% four times a day (QID) and ketotifen 0.025% twice daily (BID). The epithelial defect was scraped, and a soft bandage contact lens (BCL) was placed with ofloxacin 0.3% drops QID and cyclopentolate 0.05% BID. After 1 week of treatment, the conjunctiva was less inflamed; however, the epithelial defect failed to heal (1.6×3.1 mm) (Fig. 2). Topical CsA 0.05% in preservative-free solution eight times a day was started. After another week, the ulcer was much smaller (0.8×1.6 mm). One week later the epithelium was almost healed, with a remaining 0.5×0.5 mm defect. The conjunctiva was still hyperemic; nonetheless, the cobblestone papillae and the limbus seemed quieter, and the mucus discharge resolved. Over the next 10 days, the prednisone drops were tapered to 1 per day and CsA to 6 per day. A small epithelial defect remained for 4 weeks after the commencement of CsA treatment. After 3 months, the epithelium was completely healed, with a stromal scar. The VA was 0.5. The patient reported no pain or irritation/itching; there was no conjunctival hyperemia or mucus. The patient continued using CsA drops six times a day, prednisone drops once a day, and ketotifen drops BID. A year later, CsA drops were gradually reduced to BID, no recurrence of the vernal shield ulcer was seen. Eventually CsA and prednisone drops were stopped, and the patient only continued on ketotifen drops. Five years later, uncorrected VA was 1.25, and corneal scarring at the peripheral superior cornea was barely visible at slit lamp examination.

Table 1 Clinical Classification of Vernal Keratoconjunctivitis. Adapted from Lapid-Gortzak et al. [11]

Palpebral	
Mild	Conjunctival papillae
Moderate	Mucus secretion
Severe	Mucus plugs, giant papillae, or symblepharon
Limbal	
Mild	Thickening or opacification of the limbal conjunctiva
Moderate	Gelatinous lymphatic nodules (Horner-Trantas nodules)
Severe	Hyperemia, redness of the conjunctiva with corneal pannus formation
Combined	Limbal and palpebral, all with corneal involvement
Corneal	
Mild	Superficial punctate keratopathy
Moderate	Nebulous keratopathy
Severe	Shield ulcer



Fig. 1 Giant papillary conjunctivitis with mucus

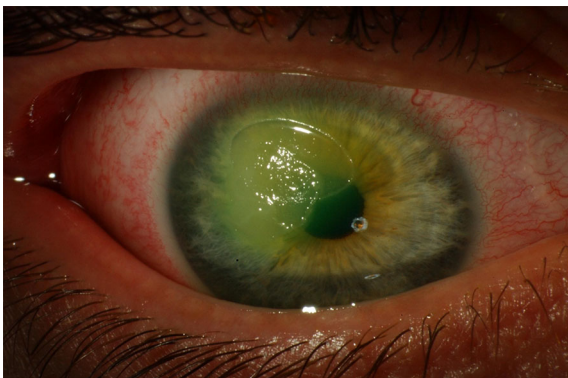


Fig. 2 Shield ulcers

Patient 2

A 15-year-old boy had been under treatment since the age of 5 years for distichiasis and trichiasis secondary to irradiation for acute lymphoblastic leukemia at the

age of 2 years. He was treated with repeated cauterization, electrolysis, and oculoplastic procedures. At the age of 15 years, he was diagnosed with VKC. He presented with a severe VKC with giant papillae, mucus discharge, and punctate corneal erosions. Initial treatment consisted of topical ketotifen 0.025% BID, dexamethasone 0.1% BID, and artificial tears. After an interval without treatment, an epithelial defect of 2.5×4 mm was noted in the center of the left cornea, with a macropannus and stromal neovascularization. The VA was 0.2. The patient was initially treated with a BCL and non-preserved chloramphenicol 0.4% drops QID, as the defect was thought to be due more to trichiasis, post-radiation keratopathy, and exposure than to an allergic disorder. After 1 month of treatment, the epithelial defect measured 1×2 mm, with fibrin and mucus deposits at the bottom of the ulcer. Referral to a cornea specialist yielded the diagnosis of a shield ulcer (grade 2) and topical CsA 0.05% eight times per day was added. After 2 weeks of the treatment a marked improvement was noted; the conjunctiva seemed much less hyperemic; the cornea looked more clearer; however, the ulcer did not decrease in size. Tapering down of CsA lead to another small defect, adjacent to the first one. The treatment was intensified again, topical CsA 0.05% was increased to eight times a day and prednisone 1% drops hourly were added. After 2 weeks, the defect was closed. Gradual tapering of the eye drops did not lead to recurrences and the patient remained asymptomatic on the CsA and prednisolone BID. On slit lamp examination, there was no conjunctival hyperemia, nor limbal edema. The VA restored to 0.5. After

5 years of follow-up with chronic treatment with CsA BID, the shield ulcer has not returned; the VKC is under control; and the uncorrected VA is 0.5.

Patient 3

A 7-year-old boy was referred to our out-patient department with vernal keratoconjunctivitis and a shield ulcer in the right eye. The boy had a 3-month history of itchiness and pain in both eyes. Prior to referral, the patient was treated with olopatadine 0.1% drops BID, prednisolone 0.5% drops QID, and ofloxacin drops three times daily (TID) into both eyes. On presentation, the VA was 0.2 in the right and 0.8 in the left eye. Upon eversion, giant papillae were noted on the tarsal conjunctiva of both upper eyelids, and some mucus was seen in the fornices. Diagnosis of severe VKC was made. The limbus was flat and quiet; however, the conjunctiva was hyperemic, and the right eye had a central shield ulcer (grade 2) of 3.9 mm × 6.8 mm, with deposits and debris. The treatment was altered to unpreserved prednisolone 0.5% drops eight times per day, CsA 0.05% eight times per day, and unpreserved ketotifen 0.025% BID. A BCL was placed. Additionally, oral desloratadine 2.5 mg once a day was initiated. After a week of the above-mentioned treatment, the shield ulcer was smaller (3.5 mm × 6.5 mm) and more clearer, with less dense debris. Also the conjunctiva was quiet, with no mucous discharge. Two weeks after the initiation of the treatment, the plaque was completely epithelialized. A white sub epithelial plaque remained however. This was surgically debrided after 1 month because recurrent epithelium erosions occurred over the plaque.

Two months later, the patient developed an opacified shield ulcer (grade 2) in the left eye. The ulcer measured 2.52.5 mm. VA was 0.3. After 2 weeks of treatment with CsA 0.05% eye drops eight times a day (added to prednisolone 0.5% drops TID and ketotifen 0.025% BID), the shield ulcer decreased in size to 1.0 × 1.0 mm. After 3 weeks of treatment, there still was a small ulcer with residual mucus and opacification. We decided to surgically remove the plaque. After this, the epithelium defect restored within 4 days. Residual corneal scarring after the shield ulcers re-epithelialized is shown in Fig. 3.

CsA 0.05% eye drops were continued for up to QID, while prednisolone was only needed every other

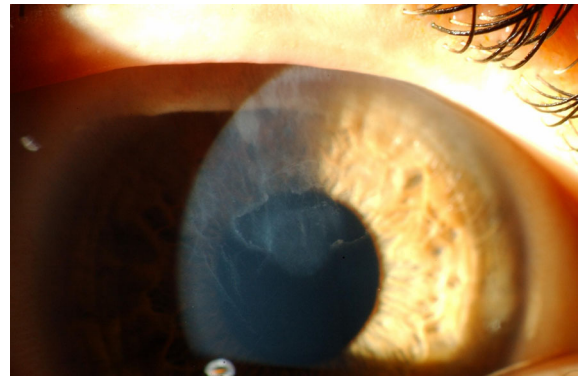


Fig. 3 Healed shield ulcers

day. Ketotifen 0.025% was continued BID. VA restored to 1.0 in both eyes.

See also Table 2 for patient characteristics.

Discussion

Corneal complications of VKC are potentially vision threatening and require immediate attention. The pathophysiology leading to the corneal damage is still not fully understood; however, it has been shown that the fibroblasts of the cornea and conjunctiva activated by the Th2-derived chemokines promote the recruitment and activation of eosinophils and Th2 cells on the ocular surface. Subsequent degranulation of eosinophils with the release of cytotoxic substances as well as the production of matrix metalloproteinase by activated fibroblasts leads to the cornea damage with the deposition of plaque-like debris from eosinophils and epithelial cells [12].

Topical steroids in combination with anti-histamines and artificial tears are the most commonly used therapeutic options in patients with VKC [13]. However, topical steroids are associated with potential side effects, such as increased intraocular pressure, cataract formation, and superinfection [14]. Moreover, steroid resistant forms can be encountered, especially the most severe ulcers with plaque formation, and delayed epithelialization which necessitate an alternative therapy [13]. In those cases, a surgical debridement, excision, or cryotherapy of the giant tarsal papillae with or without supratarsal steroid injection has been described. Such treatment, however, does not have a long-term immunosuppressant effect, and therefore, it does not inhibit the immune-mediated destruction of

Table 2 Patient characteristics

Patient	Size of shield ulcer (mm)	Grading VKC (see text)	Grading shield ulcer (see text)	Frequency of CsA 0.05% application (drops/day)	Duration till full epithelialization (days)	Frequency of CsA maintenance treatment (drops/day)	Visual acuity (Snellen) before treatment	Visual acuity (Snellen) after treatment
1	3.1 × 1.6	Severe	1	8	14	0	0.05	1.25
2	2.0 × 1.0	Severe	2	8	14	2	0.2	0.5
3 Right	6.8 × 3.9	Severe	2	8	14	4	0.2	1.0
3 Left	2.5 × 2.5	Severe	2	8	25	4	0.3	1.0

the cornea tissue and can lead to conjunctival scarring, pigment alterations of the eye-lid skin, and atrophy of the tissue [13].

Cyclosporine, a hydrophobic cyclic polypeptide isolated from the fungus *Tolypocladium inflatum*, acts as an immunomodulator. It has been shown to inhibit the proliferation and differentiation of T-cells and to abolish the T-cell signal transduction and gene transcription with subsequent decrease in the production of various cytokines including IL-2 [15]. CsA has also been found to inhibit the eosinophilic infiltration of the conjunctiva in animal models [16]. These T-cell blocking mechanisms provide more specific and additional effect on the classic treatment effects of steroids. Steroids are known to inhibit inflammatory reaction in a wider fashion by blocking the cyclooxygenase pathway and initiating lipocortin-1 production. Multiple clinical trials have provided evidence on the efficacy of CsA in VKC with no adverse effects reported except for burning and irritation [17]. However, there are only three reports in the literature on topical CsA use in the treatment of shield ulcers [7, 9, 10].

Cetinkaya et al. [7] concluded that 1% CsA in olive oil solution QID was a minimal effective concentration for the management of shield ulcers, and they observed rapid resolution of the shield ulcers within 10 days after adding treatment with CsA drops. Kumar [9] administered 0.05% 8 times per day using commercially available CsA oil- in-water emulsion (Restasis, Allergan) obtaining complete resolution of an ulcer within 3 weeks. The author concluded that more frequent instillation could compensate for lower concentration. Caputo et al used topical CsA 1% QID in addition to surgical debridement, this combined treatment showed good response in four patients.

As shown in our last case, additional scraping of the ulcers was needed to help the cornea re-epithelialize. The rationale for scraping is to remove the inflammatory material and debris in the base of the ulcer, which is thought to be composed of several cationic proteins secreted from activated eosinophils and possesses cytotoxic properties preventing wound healing and re-epithelialization [18]. The inhibition of T-cell transduction due to the treatment with topical CsA might prevent recurrences after surgical scraping. Cameron [2] showed that re-epithelialization of shield ulcers can take up to 63 weeks if left without scraping. Scraping improved healing time to 10–28 days, with a mean of 17 days. Also in our case, quick resolution (within 4 days) of the shield ulcer was observed after scraping.

From the good results shown in our patients, one might postulate that more frequent installation of topical CsA leads to supersaturation of the IL-2 receptors blockage in the conjunctiva, hereby reducing local inflammation. Also, more frequent installation of CsA might lead to more apoptosis of fibroblasts and thereby reducing the cytotoxic proteins in the base of the shield ulcer, eventually leading to faster re-epithelialization [8, 13]. The combination of the scraping of the bottom of the ulcer with the frequent installation of Cyclosporin drops is, in our opinion, the most important intervention in patients with VKC.

We report on three patients with shield ulcers due to VKC who respond quickly with complete re-epithelialization after adding topical eight times a day CsA 0.05% treatment to conventional treatment including steroids. We observed complete resolution of the shield ulcers without complications as opportunistic infections. In one case, also scraping of the ulcer was needed for re-epithelialization to take place. Tapering

the treatment to 2–6 times a day prevented recurrences for 5 years.

Conclusion

The results of high frequency CsA instillation are promising, but the different dosages and installation frequencies of topical CsA should be evaluated in a prospective way to elucidate which therapeutic scheme is most beneficial.

Compliance with ethical standards

Conflict of interest None. Dr. Lapid is a clinical investigator for Alcon and Hanita lenses, a speaker for Alcon, Hanita Lenses, and Santen, and a consultant for Alcon, Eye Yon, Hanita lenses, Sanoculis, Santen and Icon.

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