



# Corneal complications of vernal keratoconjunctivitis

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## Purpose of review

Vernal keratoconjunctivitis (VKC) is a severe bilateral chronic allergic inflammatory disease of the ocular surface. In most of the cases, the disease is limited to the tarsal conjunctiva and to the limbus. However, in the more severe cases, the cornea may be involved, leading to potentially sight threatening complications. Prompt recognition of these complications is crucial in the management of VKC, which is one of the most severe ocular allergic diseases.

## Recent findings

A vicious cycle of inflammation occurs as a result of a set of reciprocal interactions between the conjunctiva and the cornea, which results in damage to the corneal epithelium and corneal stroma, and to the formation of shield ulcers and plaques, infectious keratitis, keratoconus, scarring, and limbal stem cell deficiency. These corneal complications can cause permanent decrease or loss of vision in children suffering from VKC.

## Summary

Corneal complications in VKC are the result of an on-going process of uncontrolled inflammation. Proper recognition of the corneal complications in VKC is crucial, as most of these can be managed or prevented by a combination of medical and surgical measures.

## Keywords

allergic conjunctivitis, allergic inflammation, keratoconus, shield ulcers, vernal keratoconjunctivitis

## INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic severe allergic inflammatory disease of the ocular surface in children and young adults [1]. The disease is prevalent in dry hot climates, specifically at the Mediterranean basin, the Middle East, Central and West Africa, India, and South America. It is more prevalent in boys, starts during the middle of the first decade of life, and resolves after puberty [2]. The disease is characterized by constant ocular irritation, frequent eye rubbing, photophobia, tearing, mucous discharge, and droopy lids. The signs of the disease are mostly confined to the conjunctiva, and include giant papillary reaction of the upper tarsal conjunctiva, and limbal hypertrophy or limbal infiltrates and nodules. Many times there is a combination of the involvement of the upper tarsal conjunctiva and of the limbus.

Interestingly, the cornea may be affected in the more severe forms of the disease, leading to complications that may cause permanent visual compromise. The cornea is affected as a result of the frequent mechanical injury caused by the rough surface of the giant tarsal papillae of the upper tarsal conjunctiva, which may disrupt the corneal

epithelium. In addition, the inflammatory mediators that are secreted by the activated eosinophils and mast cells may further cause damage to the corneal epithelium.

This constant damage to the cornea may cause severe complications, including shield ulcers and vernal plaques, keratoconus, corneal scarring, microbial keratitis, and limbal epithelial stem cell deficiency. As some of these complications occur during the first decade of life, they may result in amblyopia. The present review will describe the prevalence, clinical appearance, and outcome of these severe corneal complications of VKC.

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## KEY POINTS

- Reciprocal interactions between the conjunctiva and cornea in VKC cause disruption of the corneal epithelium and augment the allergic inflammatory cascade.
- Shield ulcers and plaques occur as a result of degradation of the corneal epithelium and stroma, with deposition of eosinophil-derived mediators at the base of the ulcers.
- Keratoconus and keratoconus-like topographic patterns are frequent in children with VKC, and are a result of frequent eye rubbing and tissue degradation by inflammatory mediators.
- Treatment of the corneal complications includes aggressive topical anti-inflammatory therapy, combined with surgical procedures such as superficial keratectomy for shield ulcers and corneal cross linking for progressive keratoconus.

## PATHOPHYSIOLOGY: CONJUNCTIVAL INFLAMMATION AND CORNEAL COMPLICATIONS

The cornea and conjunctiva are adjacent tissues that participate in the complex network of allergic responses in VKC, and were shown to influence each other [3]. Cells and mediators that participate in ocular allergic inflammation cause changes in both of these tissues, and the reciprocal interaction between the cornea and conjunctiva augments the inflammatory cascade of reactions and tissue damage.

The corneal epithelium has a barrier function, which secludes the corneal stroma and corneal keratocytes from the inflammatory environment of the conjunctiva. However, this barrier function may be damaged in VKC. Eosinophils and eosinophil-derived factors are responsible for the evolution of corneal ulcers. The two granule proteins that are secreted from activated eosinophils are Major Basic Protein and Eosinophil Cationic Protein. These two proteins are cytotoxic to corneal epithelial cells *in vitro*, and inhibit corneal epithelial wound healing in an organ culture model [4,5], and are found at the base of shield ulcers and plaques in VKC [6,7]. In addition, eosinophils secrete matrix metalloproteinase (MMP)-9, which degrades components of the corneal basement membrane and corneal stroma. MMP-9 is also found in the tear fluid of patient with VKC [8]. Taken together, eosinophil-derived granule proteins and the matrix-degrading enzymes are responsible for the corneal complications in VKC, mainly the corneal shield ulcers and plaques, and

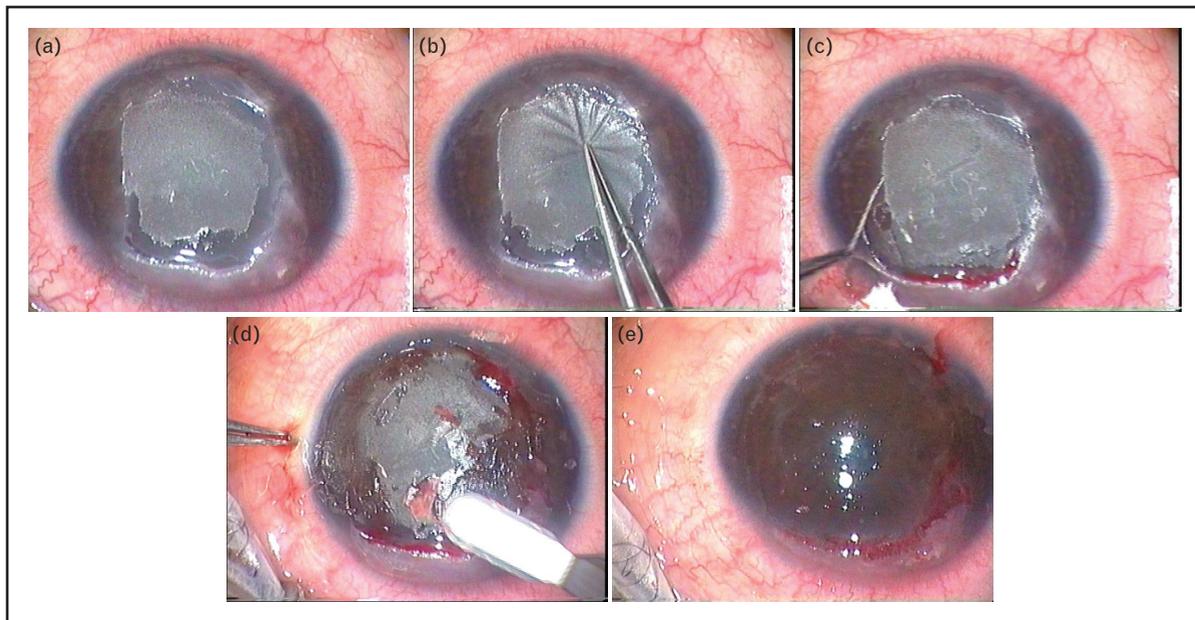
probably contribute to the formation and progression of keratoconus.

The corneal epithelial cells act as a physical barrier to prevent penetration of inflammatory mediators to the stroma [3]. Following the damage to the corneal epithelium and the disruption of its barrier function, the corneal fibroblasts become exposed to the effects of the various allergic inflammatory mediators. Corneal fibroblasts express receptors for the Th2 cytokines, interleukin (IL)-4, and IL-13, which participate in allergic inflammation [3]. In addition, these cells produce eotaxin-1 in response to the Th2 cytokines. Corneal fibroblasts also release CCL 17, an important chemokine for Th2 cells, in response to stimulation with IL-4, IL-13, or tumor necrosis factor- $\alpha$  [9]. Thus, the corneal fibroblasts may augment conjunctival allergic inflammation. Removal of the corneal epithelium in a rat model augmented late phase clinical signs conjunctival eosinophilia, and this in turn delayed corneal epithelial wound healing [10].

Taken together, these findings demonstrate a vicious cycle that link conjunctival inflammation with corneal complications in VKC, as these two processes augment each other. Eosinophils and Th2 lymphocytes produce mediators such as the eosinophil-derived granule proteins, MMP-9, and Th2 cytokines. These mediators impair the function barrier of the corneal epithelium, creating shield ulcers. As a result, the stromal fibroblasts are exposed to these inflammatory mediators, are activated, and secrete chemokines that in turn further activate the Th2 cells [3,10]. This causes a prolonged process of inflammation that augments itself, and is responsible for the various corneal complications that will be described in this review.

## SHIELD ULCERS AND PLAQUES

Shield ulcers and plaques in VKC usually evolve at the upper third of the cornea. The reported incidence among patients with VKC is 3–11%, with a subsequent permanent reduction in visual acuity in 6% of all patients [1]. In a recent large series of shield ulcers from India, the overall incidence of ulcers among patients with VKC was 4.6%, and the annual incidence ranged from 3 to 8% [11]. These are chronic epithelial abnormalities, which result from a combination of two mechanisms [6,11]. The first is the mechanical damage caused by the constant friction between the giant papillae of the upper tarsal conjunctiva against the upper third of the corneal epithelium. The second mechanism involves secretion of inflammatory mediators from activated eosinophils, which infiltrate the conjunctiva. These mediators include the Major Basic



**FIGURE 1.** Surgical removal of a shield ulcer with an opaque plaque. (A and B) Preoperative appearance; (C) removal of the adjacent epithelium covering the edges of the plaque; (D) scraping of the plaque material; and (E) after complete removal of the plaque.

Protein and the Eosinophil Cationic Protein, which are toxic to the corneal epithelium [6]. The secreted proteins accumulate with time on the denuded stromal surface of the ulcer, thus forming a dense plaque, which prevents epithelialization (Fig. 1). Chronic corneal ulcers and plaques in VKC can lead to further complications such as microbial keratitis [12,13], amblyopia [12,14], and very rarely a corneal perforation [15].

The evolution of corneal ulcers and plaques was described by Cameron, who presented a large series of 66 ulcers in 55 eyes [16]. Punctate epithelial erosions, which evolve into coarse erosions, and later coalesce to form macro-erosions, precede the development of shield ulcers (Table 1). The ulcers were divided into three types: ulcers with a transparent base (grade 1), which re-epithelialize with medical treatment and may leave mild scarring;

ulcers with translucent base, sometimes with opaque white or yellow deposit (grade 2; Fig. 1); and elevated plaques with a dense opaque deposit (grade 3). Most of the ulcers develop on the central and upper portions of the cornea.

Although grade 1 ulcers epithelialize with medical treatment alone, leaving mild corneal scarring, the grade 2 and 3 ulcers epithelialize very slowly, and are associated with severe complications. These included bacterial keratitis and amblyopia [14]. Most of these patients require surgery to remove the deposits within the ulcers or the elevated plaques (Fig. 1), which usually results in dramatic healing [16]. Medical treatment includes topical treatment with mast cell stabilizers, antihistamines, topical corticosteroids, antibiotics, and lubricating eye drops, whereas surgical treatment included debridement or superficial keratectomy (Fig. 1). Amniotic membrane transplantation was used in cases that needed a secondary intervention [11]. Excimer laser photorefractive keratectomy was also used in a limited number of patients at the base of the shield ulcer following mechanical removal of all inflammatory deposits and plaque material with fast re-epithelialization following the procedure [17]. Recurrence of shield ulcers following treatment was noted in 14.5% of eyes.

### MICROBIAL KERATITIS

Microbial keratitis is one of the most severe complications of VKC [12,13,18,19], usually resulting from

**Table 1.** Development of shield ulcers and plaques [16]

Epithelial keratopathy
Punctate erosions
Coarse keratopathy
Macroerosion
Corneal ulcers
Grade 1 – Transparent ulcer base
Grade 2 – Translucent ulcer base ± opaque white or yellow deposits
Grade 3 – Elevated plaque

infection of recurrent shield ulcers [11]. The incidence of infections is 9–10% among eyes with shield ulcers, as reported in the two large series from India and Saudi Arabia [11,16]. In one of these series of infectious keratitis following shield ulcers, the most frequent bacterial isolates included *Staphylococcus epidermidis* and *Streptococcus pneumoniae*, followed by *Corynebacterium* species, *Neisseria meningitidis*, *Klebsiella pneumoniae*, and *Brevibacterium* species [11]. Fungal infections from *Aspergillus* were also anecdotally reported in patients with VKC, with or without a shield ulcer [13,18].

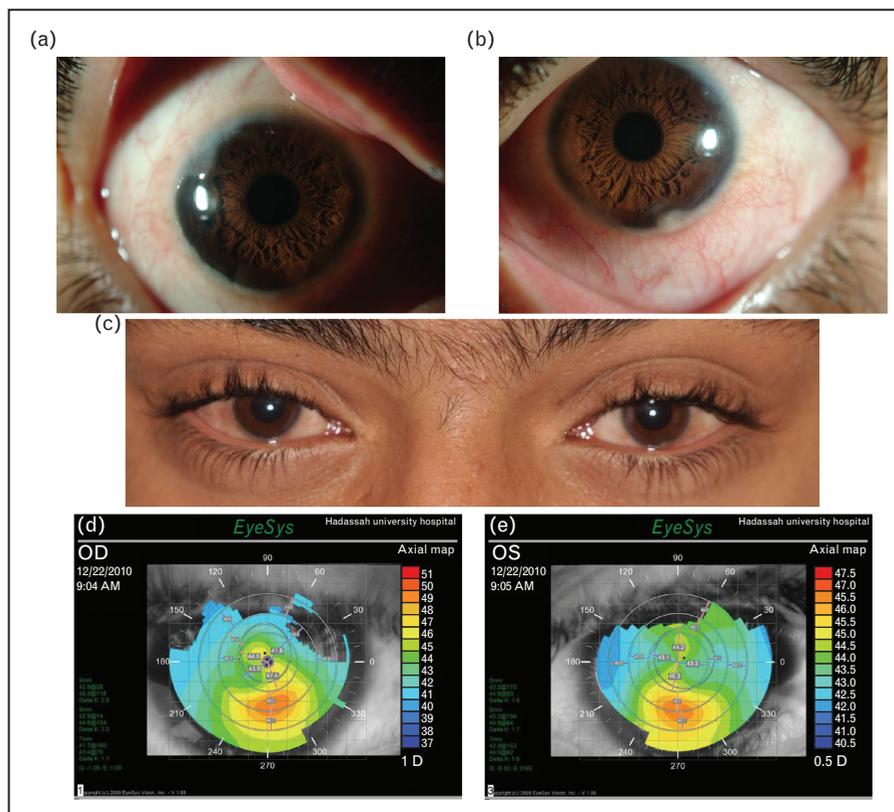
Interestingly, some of these infectious ulcers occurred while prophylactic topical antibiotic treatment was administered. In some cases of bilateral shield ulcers, bacterial keratitis occurred simultaneously in both eyes [12].

### KERATOCONUS

The association of keratoconus with VKC is well known (Fig. 2), and has been attributed to frequent eye rubbing [1,20]. The incidence of keratoconus among children with VKC was estimated as 15% in one report, and as 2.1% in a large series from Italy [2]. The incidence of acute hydrops was estimated as 6% of those having keratoconus in VKC. The reason for

this variation in incidence of keratoconus is probably a result of the topographic parameters used to diagnose this disease. In a study [21] that evaluated topographic patterns in children with VKC compared to controls, an asymmetric bow-tie (a pattern marking the shape and direction of the steep axis of the cornea) with inferior steepening was found in 31.25% of children with VKC compared with only 8.2% in healthy children. In addition, this study reported on a bow-tie with superior steepening pattern, which was found in 36.25% of the VKC patients, compared with 22.2% in controls. As this pattern is considered by many to be a normal pattern, this explains the variation in reporting on the true incidence of keratoconus. In addition, the corneal asymmetry index and the corneal irregularity index were all significantly higher compared with controls [21].

A recent study [22] from Nepal demonstrated many keratoconus-like characteristics in corneal topography of children with VKC. The incidence of true keratoconus was 11.3% (13 of 115 children with VKC). The central corneal thickness was significantly lower in VKC ( $507.2 \pm 9.8 \mu$ ) compared with normal controls ( $526.4 \pm 8.6 \mu$ ;  $P=0.00$ ). Most of the indices associated with keratoconus-like topography were found to be significantly associated with VKC.



**FIGURE 2.** An 11-year-old boy with VKC and keratoconus. (A and B) Limbal nodules and hypertrophy; (C) conjunctival hyperemia; and (D and E) corneal topography in that child demonstrating keratoconus in each eye.

The combination of frequent eye rubbing and the chronic tissue degradation of the corneal stroma from the constant exposure to inflammatory mediators are believed to cause biomechanical changes in the corneal stroma, which lead to thinning and ectasia. Using the Ocular Response Analyzer (ORA), the corneal resistance factor (CRF) was found to be significantly reduced in corneas of children with VKC compared with corneas of healthy controls [23].

Corneal cross-linking (CXL) has been the treatment of choice in preventing the progression of keratoconus over the last decade [24]. In children, the progression pattern of keratoconus is more aggressive than in adults, and hence this procedure is now strongly indicated for pediatric keratoconus [25]. As many children with keratoconus suffer also from VKC, performing CXL in these children is extremely challenging. The constant ocular surface inflammation, coupled with partial limbal stem cell deficiency may cause delay in wound healing after the CXL procedure. Therefore, these children need aggressive anti-inflammatory treatment as a preparation to CXL [25]. As of today, there is almost no literature reporting on the clinical outcome of children with active VKC and progressive keratoconus undergoing CXL.

## LIMBAL STEM CELL DEFICIENCY AND SCARRING

The chronic intense inflammation of the ocular surface that may persist for many years, coupled with the frequent rubbing of the corneal epithelium against the rough surfaces of the cobblestone giant papillae of the upper tarsal conjunctiva, all these may contribute to damage of the limbal epithelial progenitor cells, and to limbal stem cell deficiency (LSCD). LSCD was demonstrated in patients with VKC using impression cytology [26]. Patients with VKC and LSCD were older and had a longer duration of the disease compared with VKC with no LSCD [26,27]. The incidence of LSCD in VKC was reported to be 1.2% in a large series from India [27].

Corneal scarring may result from healing of persistent shield ulcers, or from healed infectious ulcers, but can also be a result of LSCD. Corneal scarring is one of the major causes for permanent visual loss in VKC. In one of the largest series from India, corneal scarring was noted to be the major complication of VKC, with an incidence of 11% [28].

## CONCLUSION

Although VKC is primarily an inflammatory disease of the conjunctiva, the cornea may be involved in a

significant number of patients, causing complications such as shield ulcers and plaques, infectious keratitis, keratoconus, LSCD, and scarring. These may cause temporary visual loss, and if not managed aggressively, may result in permanent visual loss. As treatment is available to most of these complications, it is important to recognize these problems and treat them accordingly. Surgical debridement and superficial keratectomy should be performed in grade 2 and 3 ulcers and plaques. Cultures and fortified antibiotics should be administered in infectious keratitis. Corneal cross-linking may be performed to prevent progression of keratoconus; and most important, effective topical anti-inflammatory therapy with nonsteroidal agents may prevent or reduce the morbidity which is associated with the corneal complications of VKC.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
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