

Vernal Conjunctivitis

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Vernal conjunctivitis (VC) is a bilateral, seasonal, external ocular inflammatory disease of unknown cause. VC most commonly begins in the spring, hence the name “vernal.” Afflicted patients experience intense itching, tearing, photophobia, and mucous discharge, and usually demonstrate large cobblestone papillae on their superior tarsal conjunctiva and limbal conjunctiva. VC primarily affects children, may be related to atopy, and has environmental and racial predilections. Although usually self-limited, VC can result in potentially blinding corneal complications. Treatment of chronic forms of ocular allergies may necessitate collaborative efforts between the ophthalmologist and the allergist or immunologist.

History

The first reported description of VC was in 1846 by Arlt, who reported what would be one of the classic VC presentations of perilimbal swelling, while von Graefe in 1871 reported cobblestone papillae on the upper tarsal conjunctiva. Shortly thereafter, in 1872, Saemisch observed seasonal flares of the disease in 182 VC patients and coined the term “vernal catarrh” or “spring catarrh.” Other characteristic features, such as white points at the

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limbus, were reported in 1879 by Horner (Horner's points), and further characterized by Trantas (Horner-Trantas dots) in 1899. During this time, in 1888, Emmert categorized VC into three types:

- Palpebral, with papillae primarily involving the upper tarsal conjunctiva
- Limbal, with papillae located at the limbus
- Mixed, with components of both palpebral and limbal types [1]

With the evolution of histology, Herbert, in 1903, observed eosinophils in the peripheral blood of VC patients; in 1908 Pascheff found a prevalence of mast cells in the tarsal conjunctival epithelium of VC patients [1]; and in 1909 Gabrielides reported finding eosinophils in conjunctival secretions in addition to providing a detailed description of the vernal plaque.

Epidemiology

Although VC has a world-wide distribution, it does have racial and regional variations. There is a greater prevalence of VC in hot, dry environments, such as the Middle East, the Mediterranean basin, North and West Africa, parts of India, and Central and South America [2–4]. This disease accounts for 0.1% to 0.5% of the patients presenting with ocular problems and appears to be increasing. A cross-sectional study performed in eastern Africa reported that VC affects as many as 5% of school-aged children [5], 10% of 74,400 outpatient visits to ophthalmic clinics in Israel [6], and up to 15% in Italy [4]. A recent case series from Nigeria identified VC as the most common conjunctival disease seen in a major teaching hospital over a 2-year period [7]. In that same study the association with atopy was noted to be 5%, while in another Nigerian study it was found to be as high as 20%, with approximately 6% connected to asthma, 5% allergic rhinitis, and 4% eczema [8]. The greater prevalence in hotter regions could be because of a higher level of atmospheric pollution by pollens and other allergens [1]. Seasonal variation, association with atopy, and regression of the disease are also less common in these regions. In a Japanese study, the breakdown of patients with ocular allergies included seasonal allergic conjunctivitis (SAC) (81.2%), perennial allergic conjunctivitis (10.6%), atopic keratoconjunctivitis (AKC) (4.4%), and vernal keratoconjunctivitis (VC) (3.8%), with a mean age in each disease of 52.9, 56.1, 25.7, and 16.6 years, respectively. Total clinical score, based on 10 objective ocular clinical findings of conjunctival, limbal, and corneal lesions, resulted in a progressively increasing scores of 1.54, 2.13, 3.72, and 12.68, respectively [9].

The prevalence of VC in temperate areas, such as Northern Europe, has been shown to be affected by the immigration of African and Asian children [10]. While this suggests the contribution of genetic factors to the pathogenesis of this disease, substantive work in this area is still ongoing [11].

VC is primarily a disease of childhood and youth. VC has been reported in patients as young as 1 month old to patients over the age of 70. However, the

majority of patients are between 5 and 25 years of age. Approximately 60% are between 11 and 20 years of age, 17% between 21 and 30 years of age, and 6% greater than 30 years of age [12]. The mean age of onset is between 6 and 7 years old, with a slightly earlier onset in boys than in girls [3,13]. Boys are more frequently affected than girls, with a reported ratio of 4:1 to 2:1 until puberty. By age 20 this ratio approaches 1:1 [3,13]. Recurrent episodes usually occur over a 2- to 10-year period and often resolve spontaneously around puberty. In middle-aged patients, the disease may persist and become protracted. Some of these patients develop an ocular condition that is indistinguishable from the typical atopic conjunctivitis of adulthood.

A recent case series of 128 VC subjects from the Padua region of Italy found that the incidence of VC was 1 in 100,000 for all inhabitants, regardless of age and gender. For the population under 15 years of age, the mean incidence was 7.2 in 100,000 (10 in 100,000 in males, 4.2 in 100,000 in females). In the population over 15 years of age, the mean incidence was 0.06 in 100,000 (0.04 in 100,000 in males, 0.08 in 100,000 in females) [3].

Clinical manifestation

VC is an allergic conjunctival inflammation disorder, often with secondary keratopathy. Invariably, patients complain of itching, which can be severe. In a pediatric quality of life study, the most commonly reported symptoms were itching (93%), burning (90%), redness (90%), the need to use eye drops (90%), tearing (83%), and photophobia (80%). The children's greatest concerns were limitations on going to the pool (71%), playing sports (58%), and meeting friends (58%) [14]. Discharge is common: an accumulation of ropy mucus can be found in the conjunctival fornix. Tearing, photophobia, burning or foreign body sensation, and conjunctival injection may also be prominent.

Although typically a bilateral disease, VC can present asymmetrically. Giant papillae, the classic hallmark, form on the superior tarsal or limbal conjunctiva. The papillae in the upper lid may become so severe as to cause a mechanical ptosis from their weight. White dots (Horner's points or Trantas' dots) can occur in the limbus and persist for 2 days to 1 week [15–17]. With continued inflammation, inflammatory mediators, such as eosinophilic major basic protein in the tear film, can cause epithelial toxicity, compounding the mechanical effects of the large upper lid papillae on the cornea. A punctate epithelial keratopathy may develop and, in severe cases, the epithelium can break down to form a shield-like ulcer. These corneal ulcerations are more common in children and may compromise visual acuity if scarring develops. These defects are thought to be trophic and are usually resistant to the standard treatments (lubrication, patching, bandage contact lenses). A secondary infectious keratitis also can develop. The most common corneal degenerative change from the chronic inflammation is a pseudogerontoxon, resembling

corneal arcus. Changes in corneal curvature can also result, and keratoconus may develop late in the disease course.

As the disease continues, the symptoms can progress and can become chronic or perennial. Approximately 23% of patients have a perennial form of VC from disease onset and more than 60% have additional recurrences during the winter [13].

Conjunctival signs

VC affects the palpebral and limbal conjunctiva. The cobblestone papillae characteristic of VC are easily visible with eversion of the upper lid (Fig. 1). On slit lamp examination, they are 1 mm to 8 mm in diameter, have a central core of blood vessels, and stain with fluorescein at their apices from erosion during active inflammation. Laced between and on top of the giant papillae is a ropy mucoid discharge that can form a pseudomembrane [1]. Follicles are not a feature of this disease. VC can cause a reticular subepithelial fibrosis but does not cause keratoconjunctivitis sicca and only rarely causes cicatrization of the conjunctiva (Figs. 2 and 3) [1].

Limbal signs

Limbal VC was first described by Arlt in 1846 and is more common in highly pigmented individuals. It consists of large papillae in the limbal conjunctiva. These tend to involve the superior limbus and consist of inflammatory cells rich in eosinophils at their apices. Focal areas of mucinous degeneration of epithelial cells and eosinophils form the white Horner-Trantas dots. In severe forms of limbal VC, accumulation of inflammatory cells may form a frank mound on the peripheral cornea [18]. The limbal conjunctiva also can become thickened and opacified (Fig. 4) [1].



Fig. 1. Palpebral vernal conjunctivitis. The upper tarsal conjunctiva typically has multiple large, cobblestone-like papillae interlaced with a ropy mucus discharge. (*Reprinted from Lee Y, Raizman M. Vernal conjunctivitis. Immunology and Allergy Clinics of North America 1997;17(1):33–51; with permission.*)

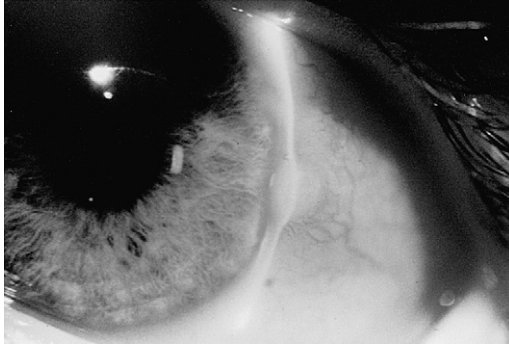


Fig. 2. Limbal vernal conjunctivitis. Large papillae can present at the corneoscleral limbus. They consist of inflammatory cells rich in eosinophils at their apices. (*Reprinted from* Lee Y, Raizman M. Vernal conjunctivitis. *Immunology and Allergy Clinics of North America* 1997;17(1):33–51; with permission.)

Corneal signs

Corneal involvement is associated with more severe disease. A superficial punctate epithelial keratopathy most commonly involves the superior half of the cornea. These can become confluent to form a shield ulcer: a shallow erosion with raised edges consisting of cellular debris and mucus. Named for their oval or shield-like shape, they tend to occur in the superior cornea and usually only affect very young patients. Mucus and fibrin can accumulate on the base of these trophic ulcers and inhibit re-epithelialization [1]. They can also scar, creating a subepithelial, gray opacity and can become vascularized with chronic corneal inflammation. With a compromised epithelial surface, these erosions are at risk for a secondary bacterial infection [19]. Shield

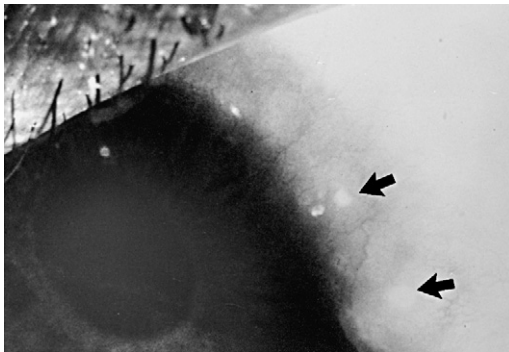


Fig. 3. Limbal vernal conjunctivitis. White Horner-Trantas dots (*arrows*) are often found at the limbus and represent focal areas of mucinous degeneration of epithelial cells and eosinophils. (*Reprinted from* Lee Y, Raizman M. Vernal conjunctivitis. *Immunology and Allergy Clinics of North America* 1997;17(1):33–51; with permission.)

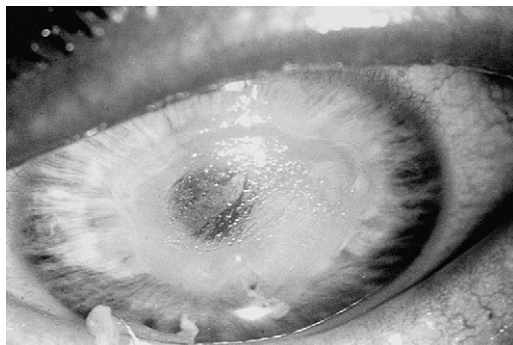


Fig. 4. Vernal shield ulcer. Named for their shield-like shape, they tend to occur in the superior cornea, are slow to re-epithelialize, and can result in visually significant corneal scarring. (*Reprinted from Lee Y, Raizman M. Vernal conjunctivitis. Immunology and Allergy Clinics of North America 1997;17(1):33–51; with permission.*)

ulcers have been reported to occur in 3% to 20% of VC cases [13,20–23]. Shield ulcers may also be complicated by amblyopia, strabismus, microbial keratitis, and corneal perforation [13,19,21,22,24].

A degenerative pseudogerontoxon resembling corneal arcus can develop in the peripheral cornea. Further degeneration can result in a peripheral furrow with steepening of the corneal curvature [25]. A superior pannus can also result from chronic inflammatory changes at the limbus.

Atypical corneal changes also have been reported in the literature. Shuler and colleagues [26] described inferior corneal ulcerations associated with palpebral VC. Cameron and colleagues [27] reported corneal ectasias (keratoconus, keratoglobus, pellucid marginal degeneration, superior marginal corneal thinning) in a series of VC patients. In general, VC rarely results in severe corneal scarring or pannus formation or other visually significant complications except for when the disease transforms into AKC (Fig. 5).

Pathogenesis

VC traditionally has been considered to be an IgE-mast cell lymphocyte-mediated hypersensitivity reaction, as suggested by its seasonal incidence, association with personal or family history of atopy, elevated levels of mast cells, eosinophils, specific IgE, and its response to antiallergic therapy [1, 28–38]. However, a large proportion of VC patients lack one or more of these characteristics. Bonini and colleagues [13] found that 42% and 47% of their cohort of VC subjects had negative skin prick and radio-allergosorbent (RAST) tests, respectively. Other studies indicate that at least 35% of VC patients lack either personal or family history of atopic conditions [39]. There appears to be a significant geographic variation as well. A large case series from Africa indicated associated atopy in as little as 5% of patients [7].

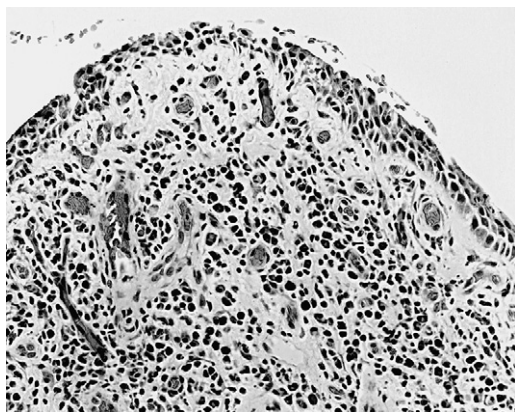


Fig. 5. Papillae from upper tarsal conjunctiva of patient with vernal conjunctivitis. Note the vascular stalks to the surface and the cellular infiltration (hematoxylin-eosin, original magnification $\times 200$). (Reprinted from Lee Y, Raizman M. Vernal conjunctivitis. *Immunology and Allergy Clinics of North America* 1997;17(1):33–51; with permission.)

Histopathologic examination of affected conjunctiva shows an increased number of mast cells, eosinophils (cells associated with allergic reactions), and lymphocytes, both in the subepithelium and epithelium [11], as well as mononuclear cells, fibroblasts, and newly secreted collagen. As the disease progresses, cellular infiltration and new collagen deposition form the giant papillae. These findings have led many to conclude that the pathogenesis of VC represents a complex interaction between the IgE-mast cell hypersensitivity and the predominantly lymphocytic type hypersensitivity, and nonspecific mechanisms [28–31,40,41].

Activation and degranulation of mast cells, whether by the classic IgE-mediated pathway or from other specific or nonspecific stimuli, play a critical role in the pathogenesis of VC and other ocular allergies. Mast cells appear to be heavily concentrated in the epithelium and subepithelial stroma [39] of VC patients. Total mast cell concentrations are also significantly greater in the substantia propria, suggesting that active recruitment of mast cells into inflamed conjunctiva plays a key role in pathogenesis [35,37].

Preformed mast cell derivatives, such as histamine and tryptase, have repeatedly been found to be elevated in VC patients [32,42–44]. Histamine is responsible for the itching and redness experienced in ocular allergy. VC patients have also been shown to respond to a histamine conjunctival challenge at a lower threshold than normal controls, which suggests a non-specific conjunctival hyperreactivity in these patients [33]. Further work has demonstrated that this hyperreactivity may be caused in part by a deficiency of histaminase, the main histamine-metabolizing enzyme, in VC patients [45]. Histamine may also play a role in the remodeling of tissues seen in VC through its stimulation of conjunctival fibroblasts, which increase

production of procollagen I and other proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-8 [46,47].

Tryptase, a neutral protease present only in mast cells, is considered a better marker for mast cell activation than histamine. Tryptase is held at a higher concentration in mast cells and is detectable for longer periods after release [43,48]. Tabbara [49] observed that tear tryptase levels were significantly decreased after medical therapy and were correlated with improvement in the clinical signs and symptoms of VC. Tabbara goes on to suggest that tear tryptase levels may serve as a good diagnostic tool for ocular allergy and for monitoring of activity of the disease. Tryptase may play its own role in VC pathogenesis through the further activation of proteases, such as metalloproteinase-2. The expression of metalloproteinases have been demonstrated in various chronic atopic disease states, such VKC, nasal polyps, and asthma, and play a role in the remodeling [50].

The release of IL-4, IL-13, and tumor necrosis factor (TNF)- α by activated mast cells has also been shown to induce production of chemokines and expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by corneal fibroblasts [51–54]. These findings highlight the importance of mast cell-fibroblast interactions in ocular allergy.

Eosinophils are found in all stages of VC and have been shown to comprise 90% of the cytologic picture in the active phase of the disease [39]. Up-regulation of eosinophils by IL-5 and fibroblast-derived chemokines, such as eotaxin [53], likely plays an important role in the corneal findings associated with VC.

Large amounts of eosinophil major basic protein (MBP) and eosinophil cationic protein have been found in conjunctiva [55] and tears [56], and significantly higher levels of eosinophil cationic protein (ECP) have been found in tears [57] and serum [58] of VC patients over controls. The levels of both mediators correlate with the severity of disease. MBP has been implicated in the pathogenesis of corneal shield ulcers [59–61]. ECP also has demonstrated epithelial toxicity [57,58]. A histopathologic study revealed granular, deeply-eosinophilic, laminar material, firmly attached to the Bowman layer that was confirmed via immunohistochemistry to be eosinophil-derived major basic protein, suggesting that MBP plaques precipitate on the denuded stromal bed, thereby playing a pathogenic role in nonhealing shield ulcers [62]. Although the corneal manifestations of VC are often described as “frictional,” from the enlarged upper lid papillae and from eye rubbing, the chemical toxicity from degranulated mast cells and eosinophils is probably a more important cause [63].

Recent attention has turned to the role of Th2 lymphocytes in the pathogenesis of VC. Bonini [41] has suggested that VC shares similarities to asthma, another Th2-driven disease. Several studies have demonstrated the abundance of Th2 cells and Th2-derived cytokines in both the conjunctiva and tears of VC patients [11,42,64–66]. Leonardi and colleagues [46]

have shown that over two-thirds of VC patients have CD4+/IL-4+ lymphocytes (Th2 cells) in tears, versus only 8% of patients displaying CD4+/INF- γ + (Th1) cells. Th2-derived cytokines (IL-3, IL-4, IL-5, IL-10, IL-13, and granulocyte-macrophage colony-stimulating factor or GM-CSF) fuel local hyperproduction of IgE (IL-4) and lead to increased levels of eosinophils (IL-5) and mast cells (IL-3). Th2 cells and their derivatives have been found in VC patients regardless of IgE allergy test results [46]. The overabundance of Th2 cells and resulting local hyperproduction of IgE may also explain an increased reactivity to nonspecific environmental factors, such as wind, sunlight, and heat [46].

Bonini and colleagues [11] have hypothesized that VC may result from an up-regulation of a “cytokine gene cluster” located on chromosome 5q, including genes for IL-3, IL-4, IL-5, IL-13 (an IL-4-like cytokine), and GM-CSF, which would further suggest that VC is a Th2 cell-driven disease. Unique genetic loci, such as the eotaxin 1 locus, have been associated with SAC [67,68], and similar genome-wide analyses for VC are now nearing completion.

Other inflammatory cells, such as neutrophils, basophils, macrophages, natural killer, and dendritic cells have also been implicated in VC through the release of proinflammatory mediators, enzymes, and cytokines [11,13,39,41,46,69–71]. In particular, leukotrienes, produced from the metabolism of arachadonic acid in mast cells, neutrophils, and macrophages, are potent mediators of hypersensitivity and inflammatory reactions [40,72,73]. Leukotriene concentrations in tear fluid have been shown to increase in allergic patients upon allergen challenge [74,75]. Leukotrienes act on the conjunctiva to produce venodilation, edema, hyperemia, and the infiltration of leukocytes and eosinophils [76–78], leading some to suggest that these compounds play a critical role in eliciting some of the common features of VC [79].

Additional areas that are currently under investigation and have demonstrated promise in animal models include immunomodulation of IL-1, IL-10, and local dendritic cells within the conjunctiva [80]. Allam and colleagues [81] have shown that early dendritic cell activation by allergens is a very early step in disease pathogenesis, with dermal allergy as the prototype.

Differences have also been noted in tear film abnormalities between VC and AKC patients. The mean tear breakup time, corneal sensitivity, and conjunctival goblet cell density values in VC patients and controls were significantly higher when compared with AKC patients. The squamous metaplasia grades in eyes with AKC were significantly higher when compared with eyes with VC and controls. The inflammatory cell response in brush cytology specimens was different between patients with AKC and VC. Eyes with AKC showed significantly higher MUC1, -2, and -4, and lower MUC5AC mRNA expression when compared with eyes with VC [82].

Other investigators have looked beyond the immune system for clues into the pathogenetic origins of VC. Substance P and nerve growth factor (NGF) receptors have been found in the tears and conjunctiva of VC patients [83–85]. Serum assays have detected high levels of both Substance P and NGF during the acute phase of the disease. In a study evaluating tear fluid Substance P levels in SAC, atopic dermatitis without keratoconjunctivitis, VC, and normal controls, found subjects with atopic dermatitis and normal controls had low levels, whereas subjects with SAC and VC showed significant elevation of Substance P [83]. Furthermore, the differential prevalence by gender and the commonly observed resolution of the disease after puberty suggests a role for sex hormones [86], as seen in other ocular inflammatory conditions, such as dry eyes syndrome [87]. Estrogen and progesterone receptors have been reported to be overexpressed by eosinophils and other inflammatory cells in the conjunctiva of VC patients [88].

Differential diagnosis

The differential diagnosis for VC must include all causes of allergic conjunctivitis [89]. Although a classic case of VC may be easily recognized, milder cases may be less obvious. Further testing may be necessary to aid in the diagnosis.

VC and AKC may be difficult to distinguish. The onset of AKC is often in the late teen years and it may persist for many years. AKC is also a bilateral disease with seasonal variations, though an association with warmer climates is less pronounced than with VC [28]. Signs and symptoms are similar to those associated with VC, including itching, burning, tearing, mucous discharge, Horner's points, corneal vascularization and ulceration, keratoconus, and pseudogerontoxon [15]. Eyelids of individuals presenting with AKC often exhibit chronic blepharitis, eczema, and secondary skin infections. In contrast to VC, AKC tends to affect the inferior palpebral conjunctiva and cause smaller papillae. AKC can cause conjunctival scarring and cicatrization, with foreshortening of the lower fornix. Neovascularization of cornea in AKC tends to be deeper, and the corneal complications are potentially blinding. In general, AKC is a more serious disease.

Seasonal allergic conjunctivitis is the most common allergic conjunctivitis. Also known as hay fever conjunctivitis, it tends to present with bilateral itching, injection, and tearing. The better-known allergens that cause SAC are pollens from ragweed, grass and trees, animal dander, and house dust. These allergens dissolve in the tear film and traverse the conjunctival epithelium to contact IgE-primed mast cells, resulting in degranulation of mast cells and release of inflammatory mediators. Rapid onset of conjunctivitis and of an allergic rhinitis or sinusitis after exposure to the allergen is characteristic of SAC. Corneal changes are rare in SAC.

Giant papillary conjunctivitis (GPC) is believed to result from allergens on foreign bodies in direct contact with the conjunctiva. Though most

widely associated with contact lenses, other irritants, such as exposed sutures and ocular prosthetics, may also cause GPC. Patients typically complain of itching, tearing, and foreign body sensation while contact lenses are worn. Giant papillae, similar to that seen in VC, can develop on the superior tarsal conjunctiva, and patients will describe a sense that the upper lid is catching the contact lens and displacing it upwards. The upper tarsal papillary response and mucus production can appear identical to VC; however, GPC will resolve with removal of the contact lens or the inciting agent.

Drug hypersensitivity can also produce a conjunctivitis that resembles VC. Common inciting agents include atropine, topical anesthetics, antibiotics, phenylephrine, glaucoma therapy, and various drug vehicles. The papillary conjunctival response tends to be less impressive and more commonly affects the inferior. Follicles tend to be more common in this condition.

Trachoma causes changes in the upper tarsal conjunctiva and superior corneoscleral limbus, which could initially appear similar to VC. In contrast to VC, however, trachoma is an infectious follicular conjunctivitis that can result in conjunctival scarring and visually significant corneal opacification. Conjunctival scraping will not contain eosinophils. VC and trachoma can present in the same patient, however, especially as these two conditions are prevalent in the same climates [90,91].

Laboratory evaluation

While the diagnosis of VC is largely clinical, laboratory testing can be helpful in differentiating VC from other forms of ocular allergy and in elucidating its various disease mechanisms [92].

Allergy testing

Allergy testing, such as skin-prick or RAST testing [36,48], have been used to identify specific triggers of VC, especially in patients with systemic allergy or atopy or in patients with a persistent disease course. However, the relatively low yield of such tests may limit their usefulness and hence they are not routinely recommended [3,13,28,30,31,89,93]. Interestingly, the tarsal form of the disease appears to be more frequently associated with allergic sensitization in both tests [3].

Conjunctival examination

Although rarely necessary, conjunctival scrapings and biopsy specimens can facilitate the diagnosis of an ocular allergic process. Because eosinophils and eosinophilic granules are not normally present in human conjunctiva, Giemsa-stained conjunctival scrapings can indicate the presence of an allergic process [48]. A conjunctival biopsy specimen can be examined by electron microscopy to identify and count mast cells, basophils, and eosinophils [48]. Light microscopy also can be used to visualize cellular

infiltration, but may not be as accurate in identifying degranulated mast cells [37].

Tear evaluation

Cytologic examination of tear fluid is relatively quick and noninvasive. The presence of neutrophils, lymphocytes, and especially eosinophils in tear fluid suggests an allergic process. While no single inflammatory mediator can be considered specific for the diagnosis of VC [94], tear evaluations will continue to provide important clues into the pathogenesis of VC. In a study of tear IgA, low levels of total secretory IgA and high levels of house dust mite-specific secretory IgA were noted, suggesting local production and a possible link to a specific allergen in the pathogenesis of VC [95] that correlates to the Israeli study, which linked house dust mite allergen to increased VKC symptoms [96]. Proinflammatory cytokines, such as TNF- α , have been found to be significantly increased in tears of VC patients when compared with controls and severity of the disease [97].

Ocular challenge test

The conjunctiva can be challenged with dry allergens or solutions placed in the inferior conjunctival fornix, or with a contact lens saturated with the allergen applied to the cornea [98]. Then, the response can be clinically observed or the tears and conjunctival scrapings can be studied for released mediators or cellular response. This test is most often used experimentally to measure mediators such as histamine, tryptase, prostaglandins, or leukotrienes in the tear fluid at different time periods after a challenge with specific allergens. It is primarily used to evaluate the therapeutic efficacy of antiallergic agents, but can be used to assess responses to specific allergens in patients with VC [48].

Leonardi and colleagues [3] performed an ocular challenge test on 103 patients, who had previously undergone skin tests for the same allergens. Of the patients tested, 59% were positive for at least one allergen. Of the patients who were negative to skin or specific serum IgE tests, 42.4% were positive to ocular challenge.

Treatment

The treatment of VC is frequently challenging and may require a multidisciplinary approach. Despite the development of new medications, VC can still be debilitating for some patients. The currently available topical drugs are effective in treating acute phases of VC [99]. It is important to remember that for most patients, the disease is self-limited with good prognosis, and iatrogenic disease should be avoided. Steroids, which are very effective in controlling inflammation, can cause complications (cataract, glaucoma, secondary infection) and should be used sparingly.

Medical treatment options include mast cell stabilizers, immunosuppressives, corticosteroids, and antihistamines. In addition to medical therapy, the successful management of VC may also require general and sometimes surgical measures. It is also important to consider the possibility that other conditions, such as blepharitis and tear film insufficiency, may coexist with VC and that they should be treated accordingly. Education of young patients and their caregivers, regarding the prolonged and recurrent nature of the disease, is a critical step toward effective long-term management.

Avoidance of all known and potential allergens may be very beneficial to the patient and can be critical for long-term stability. In certain cases, an experienced allergist can use skin and serum RAST tests to identify specific inciting allergens and can provide the education and motivation necessary for a successful environmental control program. Sometimes these adjustments will include the removal of carpeting, installation of air-conditioning and air-filtering systems in the home heating system, as well as elimination of beloved pets. Nonspecific triggers, such as sun, wind, and salt water should also be avoided with the use of sunglasses, hats, and goggles [39]. The importance of these components of total care cannot be overemphasized. Less practical but potentially helpful is a move to cooler climates during the summer months [39].

Nonspecific and medical therapy

Cool compresses, ice packs, and chilled eye drops may provide some relief, perhaps from a vasoconstricting effect or some minor role in mast cell stabilization [100]. Artificial tears can dilute allergens and mediators in the tears and may also act as an eye wash [101]. Some patients experience relief when their eyes are closed, thus making occlusive therapies (patching, occlusive goggles, or a tarsorrhaphy) helpful in some situations [2], probably by minimizing contact with airborne allergens.

Eye rubbing should be strongly discouraged, as the mechanical trauma can cause release of mast cell mediators and worsen itching and inflammation [102,103]. Soft contact lenses may help protect the eye from the mechanical friction caused by the enlarged tarsal papillae. However, soft contact lens fitting can be difficult in these patients, and the increased susceptibility to infection in patients using topical corticosteroids may contraindicate their use [2].

Mast cell stabilizers

Mast cell stabilizers represent the mainstay of therapy for VC. These agents (cromolyn sodium, lodoxamide tromethamine, nedocromil sodium, and pemirolast potassium) are thought to limit the flux of calcium across the mast cell membrane, thus preventing degranulation and release of vasoactive substances. Mast cell stabilizer therapy, two to four times daily,

should be initiated before seasonal occurrence and should continue throughout the affected season as first-line medical therapy.

Numerous studies have demonstrated the safety and effectiveness of cromolyn sodium, nedocromil, lodoxamide, and pemirolast in treating signs and symptoms of VC and SAC [36,104–110]. Additional studies suggest that mast cell stabilizers may act through other mechanisms. Cromolyn sodium reportedly inhibits the chemotaxis, activation, degranulation, and cytotoxicity of neutrophils, eosinophils, and monocytes [107,111]. Lodoxamide may exert antiallergic activity by reducing eosinophils in the conjunctiva [107]. Lodoxamide and cromolyn sodium may also have effects on Th2 cells, which have been implicated in the pathogenesis of VC [112].

A long-term comparison of nedocromil versus cromolyn sodium found that nedocromil 2% produced a more rapid and marked improvement in symptoms over cromolyn 2% and decreased the need for steroid rescue [113]. Lodoxamide 0.1% may have additional benefits over cromolyn sodium because of its anti-eosinophil action [114].

Antihistamines

Topical antihistamines, particularly those which block H1 receptors, can be useful as adjunctive therapy in mild to moderate cases of VC or in adult patients who have experienced significant improvement in symptomology since adolescence [39,86]. Topical antihistamines have been shown to reduce signs and symptoms of ocular allergy, in particular the severe itching that plagues many patients [115]. Newer agents, such as olopatadine, ketotifen, azelastine, and epinastine purportedly combine the effects of anti-H1 activity with mast-cell stabilization. However, these additional effects have not yet been validated clinically.

Systemic therapy with oral antihistamines (cetirizine, loratadine, ketotifen, oxatamide) may be beneficial given the chronicity of the disease and the potential for patients to become sensitized to preservatives in some commercial topical preparations. Patients with significant itching may benefit from hydroxyzine (25 mg–50 mg or more at bedtime), which may break the cycle of itching and scratching [2]. However, systemic antihistamines can cause or exacerbate tear film insufficiency, in which case patients should be aggressively treated with artificial tears.

Despite the symptomatic benefits experienced by select patients, both topical and systemic antihistamines often are ineffective in severe cases of VC.

Nonsteroidal anti-inflammatory drugs

Signs and symptoms of VC have been reported to improve with the addition of oral aspirin (1.5 g–4 g a day), although routine administration at these high doses could produce serious side effects, especially given that many VC patients are children [116,117].

Topical nonsteroidal anti-inflammatory drugs, such as ketorolac, diclofenac, and pronopfen, have been shown to reduce itching, ICAM-1 expression, and tryptase levels in tears associate with ocular allergy [118–120]; however their use is now limited because of the availability of newer treatment options.

Corticosteroids

Moderate to severe cases of VC that are unresponsive to mast cell stabilizers and antihistamines may necessitate the short-term use of topical corticosteroids. Corneal involvement at any stage warrants the consideration of corticosteroid therapy.

Bonini and colleagues [13] reported that 85% of patients in their long-term cohort of 195 VC patients required steroids at some point during the course of the disease. Corticosteroids diminish the signs and symptoms of ocular allergy by stabilizing capillary permeability, decreasing the influx of inflammatory cells, and inhibiting the activation and degranulation of inflammatory cells [100]. They are particularly helpful in the treatment of VC and AKC but are seldom used for GPC or SAC.

Allansmith [121] found that “pulse” therapy with topical dexamethasone (1%) given every 2 hours, eight times daily and gradually tapered over days to weeks, to be effective for breakthrough attacks of VC inflammation.

In the absence of corneal involvement, low-absorption corticosteroids, such as fluorometholone, loteprednol, and rimexolone, should be tried first. Dose and frequency are determined based on the level of inflammation, with a gradual taper occurring over 2 weeks. Only after first-line therapy fails should more potent agents like prednisolone, dexamethasone, or betamethasone be considered [39]. Supratarsal injection of short- or intermediate-acting corticosteroids has also been reported to confer relief in severe VC [122].

Active corneal signs may necessitate the initial use of prednisolone. It is critical to recognize even the mildest forms of corneal disease, as delay in treatment could result in poor visual outcome. Although pathognomonic for VC, shield ulcers often begin as a mild, nonspecific subepithelial “haze.”

Long-term maintenance, topical steroid therapy should be avoided given the potential complications, including glaucoma, formation of cataracts, and increased susceptibility to infections. Corticosteroid therapy has been associated with 2% to 7% of VC patients developing glaucoma and 14% developing cataracts [3,13,20].

Immunosuppressive agents

Cyclosporine, an immunosuppressive drug commonly used to prevent organ-graft rejection, has demonstrated efficacy in controlling ocular inflammation. Cyclosporine works primarily by blocking Th2 lymphocyte proliferation and IL-2 production [123]. It also inhibits histamine release

from mast cells and basophils and reduces IL-5 production, which may limit the infiltration of eosinophils into the conjunctiva [20,124,125]. Leonardi and colleagues [126,127] suggest that cyclosporine shows particular effectiveness in VC by reducing conjunctival fibroblast proliferation and IL-1 β production.

Cyclosporine 1% to 2% ophthalmic emulsions in olive or castor oil have been shown to be effective in the treatment of VC [128–134]. Leonardi and colleagues demonstrated that cyclosporine 2% used four times a day over 2 weeks significantly decreased signs and symptoms as well as tear levels of ECP in VC patients. Several groups have examined the effectiveness of cyclosporine at concentrations as low as 0.05%, but results at these levels have been equivocal. Spadavecchia and colleagues [135] suggest that 1% may be the lower bound for effective dosage as demonstrated in their cohort of school-age children. Leonardi and colleagues [57] found cyclosporine to have a significant steroid sparing effect, allowing VC to be controlled with mast cell stabilizers alone.

Unlike corticosteroids, cyclosporine has not been associated with lens changes or increases in intraocular pressure [133,136]. However, many patients complain of burning and irritation associated with current formulations. Other adverse events, such as bacterial or viral infections, are rare.

At present, topical cyclosporine is commercially available in the United States only as a 0.05% emulsion (Restasis). Higher concentrations must be formulated by hospital pharmacies. In Europe, phase III clinical trials have been completed for a new cyclosporine preparation, Vekacia, which is indicated for the treatment of VC. In May 2007, Vekacia also received “Orphan Drug” status by the United States Food and Drug Administration for the treatment of VC.

Other medical therapies

Lambiase and colleagues [79] have shown that montelukast, a sulfidopeptide receptor antagonist, when used for asthma treatment, also improves signs and symptoms of coexisting VC. Another immunosuppressive, Tacrolimus (FK-506), showed promise in treating VC in patients who had failed conventional therapy. However, controlled trials of this new ophthalmic application are yet to be completed [137]. Mitomycin-C has also been reported to confer benefit on VC patients [138]. Topical sirolimus has potential for topical potency, but has yet to be tested [139].

Surgical therapy

Conjunctival transposition or autografts have been performed with limited effect. Cryotherapy of the tarsal conjunctiva often provides temporary relief, possibly by decreasing the number of inflammatory cells and reducing the inflammatory mediators released; however, the papillae and symptoms usually return. Bonini and colleagues [13] have noted that cryogenic surgery

performed to reduce papillary excrescences may result in a pemphigoid-like appearance throughout the conjunctiva. Belfair and colleagues [140] have recently described the use of CO₂ laser in removing giant papillae in refractory VC. However, the long-term effectiveness of this modality is unclear. In general, conjunctival surgery is rarely required and should be avoided.

Corneal shield ulcers may respond to bandage soft contact lenses, patching, and tarsorrhaphy, in addition to the medical therapy described. Cases that do not respond to conservative measures or exhibit inflammatory deposits in the ulcer base may require surgical intervention.

Surgical debridement and superficial keratectomy can aid in the re-epithelialization of the cornea [22,141]. Daily debridement of the ulcer may promote more rapid healing. One study demonstrated rapid re-epithelialization of three central corneal lesions from VC that were treated with excimer laser phototherapeutic keratectomy. This was performed after active inflammation was controlled and the inflammatory plaque overlying the shield ulcer was removed [142].

Cameron has proposed a classification system for shield ulcers based on their clinical characteristics, response to treatment, and complications. Grade 1 ulcers had a clear base, responded favorably to medical treatment, and re-epithelialized with minimal scarring. Grade 2 ulcers had visible inflammatory debris in the base, responded poorly to medical therapy alone, and demonstrated delayed re-epithelialization with complications, such as bacterial keratitis. Grade 2 patients showed dramatic response to scraping the base of the ulcer, with re-epithelialization occurring by 1 week. Grade 3 ulcers had elevated plaque formation and responded best to surgical therapy [22].

Solomon and colleagues [62] have also reported successful re-epithelialization of the cornea after surgical scraping of vernal plaques in patients who had been nonresponsive to maximal medical therapy. Sridhar and colleagues [143] demonstrated additional benefits in combining amniotic membrane grafting with surgical debridement in a small group of VC patients. Sangwan and colleagues [144] suggest that limbal stem cell transplantation may also have promise in severe cases of VC.

Phototherapeutic keratectomy also might be useful in removing superficial corneal scars. Penetrating keratoplasty might be necessary for deeper and visually compromising corneal scars. Restoring optical clarity of the cornea would be especially critical in a young child at risk for developing amblyopia. The chronic surrounding inflammation and the tendency toward trophic erosions can make corneal transplantation particularly challenging in this young population.

Treatment of secondary infections

Secondary infection of the trophic ulcers is always a risk, especially with steroid use. These require the standard scraping and culturing of the cornea

in an attempt to isolate the organism and aggressive antimicrobial therapy. A lateral tarsorrhaphy may be helpful if re-epithelialization continues to be delayed after sterilization of the ulcer.

Hyposensitization and immunotherapy

Specific inciting allergens have been identified to correlate with VC, such as house dust mite that appears to be associated with increased VC symptoms [96], but systemic desensitization immunotherapy may be helpful in patients who are particularly sensitive to a limited number of allergens [145]. However, results are often disappointing. The effectiveness of immunotherapy for chronic ocular allergy differs from other forms of allergies, such as allergic rhinitis, asthma, and seasonal or perennial allergic conjunctivitis.

Prognosis

VC is most often a self-limiting disease, usually resolving within 2 to 10 years. Permanent conjunctival scarring is rare unless surgery was performed or unless the disease transforms into AKC. Although corneal changes, such as pannus, subepithelial scarring, astigmatism, keratoconus, and marginal corneal degeneration may be permanent, VC rarely results in diminished visual acuity that is not correctable by semirigid contact lenses or surgery. In their long-term follow-up of 195 VC patients, Bonini and colleagues [13] report that 6% of patients develop a visual impairment owing to corneal damage. Bonini and colleagues [13] also report that the size of the giant papillae is directly related to the probability of the persistence or worsening of symptoms, and that the bulbar forms of VC have a worse long-term prognosis than the tarsal forms.

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