

Vernal Keratoconjunctivitis: A Teaching Case Report

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Abstract

Vernal keratoconjunctivitis (VKC) is a relatively rare ocular disease that affects the cornea and the conjunctiva. Due to its chronic and potentially debilitating nature, early diagnosis and effective treatment are crucial. It strikes mostly children and early adolescents. Clinicians must understand the clinical signs, symptoms, and treatment alternatives to mitigate the disease progression. This teaching case report reviews the diagnosis, management, and treatment options for patients with VKC and demonstrates the importance of the clinician's role in taking a careful case history and in modifying treatment throughout care.

Key Words: *Vernal keratoconjunctivitis, allergic conjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, superior limbic keratoconjunctivitis*

Background

This case involves a 12-year-old African-American child, who presented with vernal keratoconjunctivitis (VKC). The case reflects the decision-making process used in the diagnosis and treatment of a red, itchy eye. It is appropriate for use with third and fourth year students. The case highlights the importance of obtaining a complete, accurate, precise, and relevant database during the examination. Additionally, the case demonstrates the metacognitive thinking and flexibility that clinicians utilize in the diagnosis and treatment of disease. The condition analyzed, vernal keratoconjunctivitis, is an allergic and inflammatory conjunctivitis that falls under the same umbrella class as seasonal rhinoconjunctivitis, atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC). A quick diagnosis is warranted because this disease can be uncomfortable, incapacitating, and potentially sight-threatening. Its clinical presentation often resembles other ocular conditions. Therefore, it is important for students and clinicians to be able to accurately diagnose and treat this condition

Student Discussion Guide

Case Description

Patient JS, a 12-year-old African-American boy, presented to the health center eye clinic on Aug. 27, 2005, with a complaint of bilateral red, itchy eyes for several weeks. He was seen and referred by the pediatrician at the health center. He was accompanied by his mother, who reported his last comprehensive eye examination was approximately 1 year ago. He did not wear spectacle correction. His mother reported that the pediatrician started him on erythromycin 0.5% ophthalmic ung (Ilotycin) once daily OU but switched him to olopatadine 0.1% ophthalmic solution (Patanol) b.i.d. OU after 5 days of minimal relief with erythromycin. His mother was concerned because the redness and tearing appeared to be worsening. She was worried that these symptoms were caused by a recent introduction of cats to their home. The boy reported crustiness upon awakening in the morning, as well as a watery discharge. Ocular history was unremarkable. Medical history

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was positive for G6PD deficiency, seasonal allergies, asthma, and eczema. The patient was allergic to aspirin and sulfur. Other than olopatadine, he was not taking any medications.

The impression at this visit was allergic conjunctivitis. Allergic conjunctivitis was determined from the itchy symptoms and the presence of hyperemia, chemosis, watery discharge, and mild papillae. Since the patient had come to the clinic already using olopatadine 0.1% b.i.d. OU, and it offered little relief, the mother requested an alternative eye drop. The mother insisted on a change of medication despite extensive education regarding the length of time required for the olopatadine to achieve therapeutic levels. The patient was then switched from olopatadine to ketotifen (Zaditor) b.i.d. OU. Ketotifen was chosen because it is an over-the-counter (OTC) alternative to olopatadine and has a similar efficacy profile. The patient was advised to stop rubbing his eyes and to use cold compresses whenever his eyes felt itchy. The patient was asked to return to the clinic in a week or sooner if the symptoms worsened.

Follow-up #1: 9/24/2005

The patient and his mother missed their 1-week follow-up appointment but returned 1 month later on Sept. 24, 2005. The mother reported no changes to the patient's medical history since the last eye examination. The boy reported that his eyes were still red upon awakening but that the redness improved as the day progressed. He reported no associated discharge but some crustiness remaining in the early morning. He also had symptoms of itchiness and mild tearing. Despite what was prescribed and recommended, the mother asked the patient to stop ketotifen b.i.d. a few weeks prior because she noticed no improvement in his symptoms.

The diagnosis was changed from allergic conjunctivitis to VKC OU. The diagnosis of VKC was supported by the presence of large cobblestone papillae on eversion of the superior lids, as well as superior limbal Horner-Trantas dots. Figures 1 and 2 represent the clinical signs but are not the actual patient's findings.¹ At this time, the patient was prescribed loteprednol 0.5% ophthalmic suspension (Lotemax) q.i.d. OU

Table 1
Initial presentation: 8/27/2005

	OD	OS
Distance visual acuity sc	20/25	20/20
Pupils	Pupils equal, round, and reactive to light (PERRL) negative afferent pupillary defect (APD)	PERRL-APD
Pre-auricular nodes	None palpable	None palpable
Significant anterior segment findings	Grade 1 inferior follicles/ papillae Grade 2+ hyperemia Inferior chemosis	Grade 1 inferior follicles/ papillae Grade 2 hyperemia Inferior chemosis
Lid eversion of superior lids	Grade 1 papillae inferior nasal aspect of superior lids and grade 1 follicles	Trace papillae inferior nasal aspect of superior lids and grade 1 follicles
Fluorescein staining	None	None
Intraocular pressures (GAT) @ 1:35 p.m.	15 mmHg	14 mmHg

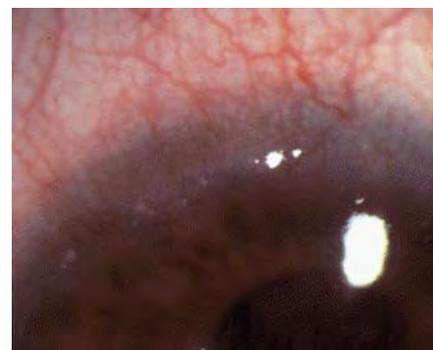
Table 2
Follow-up #1: 9/24/2005

	OD	OS
Distance visual acuity sc	20/20	20/20
Pupils	PERRL-APD	PERRL-APD
Pre-auricular nodes	None palpable	None palpable
Significant anterior segment findings	Inferior follicles and papillae in conjunctiva Grade 1+ hyperemia Superior limbal Horner- Trantas dots	Inferior follicles and papillae in conjunctiva Grade 2 hyperemia Superior limbal Horner- Trantas dots
Lid eversion of superior lids	Grade 2 cobblestone papil- lae	Grade 1+ cobblestone papillae
Fluorescein staining	None	None
Intraocular pressures (GAT) @ 12:11 p.m.	14 mmHg	14 mmHg

Figure 1:
Cobblestone papillae



Figure 2:
Limbal Horner-Trantas Dots



and was reminded to shake the bottle before each instillation. The mother and the patient were educated on the condition and were given an informational handout on VKC. They were advised on the characteristics of loteprednol, including its propensity to increase intraocular pressure with prolonged use. They were educated on the importance of follow-up visits to monitor for progression of the disease, as well as for elevation of intraocular pressure. They were advised to return in 1 week or sooner if the symptoms persisted.

Follow-up #2: 9/30/2005

The patient and his mother returned 1 week later on Sept. 30, 2005. The patient was still using loteprednol 0.5% ophthalmic suspension q.i.d. OU with the last drop instilled at 6:30 a.m. that day. He reported significant improvement in symptoms.

The patient was asked to continue loteprednol 0.5% ophthalmic suspension but to start a taper schedule of three times a day for 1 week, two times a day for 1 week and then once a day for 1 week. He and his mother were advised to return in 4 weeks or sooner with any worsening symptoms.

Follow-up #3: 11/22/2005

At the 2-month follow-up visit, all ocular signs and symptoms had resolved. The patient had since tapered and discontinued loteprednol in both eyes.

The diagnosis at this visit was resolved VKC OU. The mother and the patient were educated on the chronic nature of the condition and on the possibility for recurrence, remissions, and exacerbations over time. They were asked to return to the clinic at the earliest onset of symptoms or prior to the allergy season next year so the patient could be started on a preventative eye drop, such as cromolyn sodium.

Key Concepts

1. The pathophysiology of allergic ocular diseases
2. The assessment of hallmark symptoms in diagnosing VKC
3. The role of epidemiology and differentiating VKC from other forms of allergic or immunologic ocular conditions

Table 3
Follow-up #2: 9/30/2005

	OD	OS
Distance visual acuity sc	20/20	20/20
Pupils	PERRL-APD	PERRL-APD
Pre-auricular nodes	None palpable	None palpable
Significant anterior segment findings	Few inferior follicles and papillae Trace hyperemia Superior limbal Horner-Trantas dots	Few inferior follicles and papillae Trace hyperemia Superior limbal Horner-Trantas dots
Lid Eversion of superior lids	Grade 1 cobblestone papillae	Grade 1+ cobblestone papillae
Fluorescein staining	None	None
Intraocular pressures (GAT) @ 3:45 p.m.	13 mmHg	14 mmHg

Table 4
Follow-up #3: 11/22/2005

	OD	OS
Distance visual acuity sc	20/20	20/20
Pupils	PERRL-APD	PERRL-APD
Pre-auricular nodes	None palpable	None palpable
Significant anterior segment findings	All clear	All clear
Lid eversion of superior lids	Clear	Clear
Fluorescein staining	None	None
Intraocular pressures (GAT) @ 2:10 p.m.	13 mmHg	13 mmHg

4. The importance of appropriate follow-up care
5. The significance of approaching diagnosis and treatment with flexibility and a willingness to revise the diagnosis and treatment plan as needed

Learning Objectives

1. To identify and list the basic signs and symptoms of VKC
2. To describe the demographics, including age, sex, race, and location or origin of the disease
3. To be able to differentiate between other similar clinical entities
4. To understand management and treatment options at various stages

of the disease process.

5. To describe and understand the underlying immunological cause of VKC

Discussion Questions

- A. Knowledge, Concepts, Facts, Information Required for Critical Review of the Case
 1. Describe the classic signs and symptoms of allergic eye disease versus VKC and discuss how they differ.
 2. Describe the immunological classifications of allergic and inflammatory ocular diseases.
 3. Discuss the disease process at the cellular level, relating the

ocular structures and physiology to the signs and symptoms of VKC.

4. Discuss the general risk factors for VKC and compare them with the patient's individual risk factors.
5. Determine the differential diagnosis in this case based on analysis of case history, risk factors, and demographics.
6. Describe the pathophysiology of the disease process.
7. Describe the mechanisms of action of the pharmaceutical agents involved.
8. Discuss how the recent acquisition of a cat impacted the case?

B. Generating Questions, Hypothesis, and Diagnosis

1. What diagnostic tests were used in this case to diagnose VKC?
2. How were the clinical findings and information analyzed to rule out or support the potential differential diagnosis in this case?
3. What evidence or information is needed to diagnose VKC?
4. How does one differentiate between VKC and other diseases, such as AKC or allergic conjunctivitis?
5. After analysis of the information, what is the best possible diagnosis at this time?
6. Is the diagnosis logical?
7. At this time, are there other diagnoses one should consider?

C. Management

1. What are the classes of medications used to treat VKC?
2. What is the goal of treatment and care for the patient?
3. What is the prognosis for a patient with VKC?
4. What is an appropriate follow-up schedule?
5. What happens when symptoms worsen or do not improve?

6. When should treatment plans be modified?
7. What preventative environmental measures can be useful for managing VKC?
8. What is the role of a physician or allergist in the management of patients with chronic allergic disease?

D. Critically Assessing Implications, Patient Management, and Psychosocial Issues

1. What are the implications of treatment versus no treatment? Consider cost, time, side effects, convenience effect, and quality of life.
2. What are the consequences associated with noncompliance to the treatment plan?
3. What pertinent information should be used to educate family members regarding the condition?
4. Discuss appropriate responses to a patient's or family member's anxiety toward the ocular condition, perceived medication failure, long-term disease consequences, risks associated with medications, etc.

Educator's Guide

The educator's guide includes the necessary information to discuss the case.

Literature Review

Vernal keratoconjunctivitis is an allergic and inflammatory conjunctivitis that falls under the same umbrella class as seasonal rhinoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis.^{2,3} The term keratoconjunctivitis is appropriate to use because VKC can affect the cornea and the conjunctiva. It can involve either the superior tarsal or limbal palpebral conjunctiva or both (mixed).^{2,4} Interestingly, the limbal (bulbar) form of the disease is more prominent in tropical climates and in dark-skinned races, while the tarsal form is more prevalent in temperate areas and in lighter-skinned races.^{2,5} VKC can lead to cornea changes in the form of shield ulcers. A shield ulcer is an ulcer commonly found on the superior cornea as a result of the mechanical abrasion of the lids to the cornea.² Al-

though it can occur unilaterally, VKC is typically a bilateral disease and can affect one eye to a greater extent than the other.⁶

VKC predominantly affects African Americans and shows a 3:1 gender predilection toward boys.⁶ Although it can occur at any age, it is most common in patients between 3 to 25 years of age, with 7 years as the average age of onset. It can last anywhere from 5 to 10 years.⁶ VKC often strikes during warm, temperate weather; hence, the term vernal meaning spring-time is used. The term is a bit of a misnomer, however, as patients can get it year round and can have recurrences during other seasons.⁵ For instance, approximately 23% of patients have the perennial form, and more than 60% of patients have additional recurrences in the winter.⁷ Patients often have associated medical history of atopic diseases.⁸ For instance, more than 50% of patients have concurrent medical history of asthma, rhinitis, or eczema, with asthma being the most common atopic disease associated with VKC.^{4,7} It is uncertain if family history plays a role in the disease process, as only 35.3% of VKC patients have a family history of allergic diseases.⁵

The hallmark symptom of VKC, like all allergic eye disease, is itching.⁵ Symptoms of VKC vary and can include foreign body sensation, tearing, photophobia, and thick ropy discharge.^{5,8-10} A foreign body sensation results from conjunctival surface irregularity and mucous secretions, while severe pain is usually caused by a compromised cornea, typically from superficial punctate keratitis, epithelial macroerosions, or ulcers and plaques.⁵

Patients often present with signs of conjunctival redness, giant papillae, pseudoptosis, and superficial keratitis.¹¹ Hallmark signs include cobblestone papillae (greater than 1 mm and up to 7-8 mm in diameter) and Horner-Trantas dots, which are gelatinous limbal infiltrates.^{4,6,8,9} The papillae enlarge and have a flat-topped polygonal appearance similar in appearance to cobblestones.² Limbal VKC is characterized by mucoid nodules that have a round, smooth surface surrounded by discrete, white superficial spots around the limbus.² Persistent or recurrent limbal disease could lead to pannus or corneal

opacification (pseudogerontoxon).^{12,13} A pseudogerontoxon is a lesion that resembles a small segment of arcus senilis and is sometimes the only indication of prior allergic eye disease.¹³ Punctate keratitis, followed by macroerosions, plaques, and subepithelial scarring can also be seen. Punctate epithelial erosions can evolve into corneal shield ulcers in advanced cases.^{8,12} The ulcers and scarring can cause irregular astigmatism that may lead to a reduction in best-corrected visual acuity.¹¹ Neovascularization of the superior cornea as well as blepharitis and maceration of the lids can ensue.⁸ Cataracts and steroid-induced glaucoma are more serious complications that can also result from VKC.⁸ A quick diagnosis is warranted, as this disease can be uncomfortable and incapacitating. The severity of symptoms, such as extreme photophobia, often forces children to live virtually in the dark.⁵

Most studies note that the size of the cobblestones is directly related to the persistence or worsening of symptoms, with larger papillae having a worse long-term prognosis.⁴ There are mixed findings in the literature regarding the form of VKC with the worse prognosis. Some studies state that the bulbar form of VKC has a more severe long-term prognosis while other sources indicate the tarsal form does.^{4,9} Horner-Trantas dots in the limbal form of VKC are formed when degenerated eosinophils aggregate in the peripheral cornea.⁹ In extreme cases, vernal shield ulcers can be formed by abnormal mucous, fibrin, and serum deposition on the superficial corneal epithelium.⁹ These epithelial erosions are caused by a combination of the inflammatory chemicals and mechanical rubbing of the papillae over the cornea.⁹

Diagnosis of VKC is usually made by obtaining a careful case history, conducting a thorough physical examination, and on clinical judgment based on the signs and symptoms. Conjunctival scrapings, which demonstrate the presence of infiltrating eosinophils, may be necessary for some difficult cases.⁸ Total and specific immunoglobulin E (IgE) determination is not entirely useful, however, because more than 50% of patients with VKC present with negative findings.⁸

Differential diagnoses and treatment options for VKC:

- Allergic conjunctivitis, both seasonal and perennial, is caused by the typical immunoglobulin E (IgE)-mediated reaction to environmental allergens, such as grass and tree pollens, mites, mold, and animal dander.¹⁴ Patients with the diagnosis often have concurrent allergies, including runny nose, sneezing, and asthma. Symptoms include itchy, watery eyes.¹¹ Signs include red, edematous eyelids, chemosis, and conjunctival papillae. Olopatadine, ketotifen, azelastine (Optivar) and epinastine (Elestat), which are antihistamine medications that have significant mast-cell stabilizing effects, are commonly used to eradicate the symptoms.¹⁵
- Atopic keratoconjunctivitis (AKC) is far less common than seasonal allergic conjunctivitis and can be potentially blinding when left untreated. Patients often have atopic dermatitis or eczema and present with eyelids that are red, scaling, and weeping.¹⁴ Although papillae are also found in AKC patients, they are usually smaller than in VKC. The conjunctiva usually has a milky edema.⁶ The signs are more prominent in the lower conjunctiva, different from VKC, in which the signs are more prominent in the upper conjunctiva.¹⁶ Treatment for AKC involves antihistamine creams, corticosteroid creams, cromolyn sodium eye drops, and cold compresses.¹⁵
- Giant papillary conjunctivitis (GPC) is an allergic response that is not considered a real allergic disease, but rather a chronic microtrauma.¹⁴ It affects the upper lids more than the lower lids. Although there are different causes for GPC, including irritation from prosthesis, foreign body, or exposed sutures, the most common is mechanical irritation from soft contact lenses.⁶ Signs include itching, ropy discharge, blurry vision, and pain with contact lens use.⁶ Treatment usually involves discontinuing contact lens wear and using artificial tears and topical agents, such as cromolyn sodium, lodox-

amide (Alomide), olopatadine, and steroids, such as loteprednol (Lotemax or Alrex).⁶

- Superior limbic keratoconjunctivitis (SLK) is a chronic inflammatory disorder affecting mostly middle-aged women. A large percentage of patients, approximately 20% to 50%, have an associated thyroid dysfunction. Patients present with foreign body sensation, burning, photophobia, and mucoid discharge. Signs include papillary hypertrophy of the superior tarsus, hyperemia of the superior bulbar conjunctiva, papillary hypertrophy at the limbus, and punctate epithelial erosions of the superior cornea.² Close inspection usually reveals a sectoral inflammation and injection of the superior bulbar conjunctiva.¹⁵ Treatment involves tactics to alter the abnormal mechanical interaction of the upper eyelid and the superior corneal limbus. This may involve topical medications, such as artificial tears, occlusion of the upper puncta, and soft contact lens wear. In resistant cases, thermocauterization of the superior bulbar conjunctiva, as well as resection of the superior limbal conjunctiva may be performed.²

Discussion

Ocular allergies are a detriment to society. Their prevalence is increasing worldwide, and they are known to affect more than 20% of the population in the United States. Severe forms, such as VKC, hinder vision and quality of life.¹⁷ Numerous factors, such as genetics, air pollution, pets, and household dust can contribute to ocular allergies.¹⁷ Ocular allergies are not only distressing to patients but they have contributed to increased health care costs. For instance, the health care cost related to allergic rhinoconjunctivitis has been reported to be \$5.9 billion in the United States, with 25% of this cost resulting from medication use.¹⁷

The ocular allergic response is complex. It results when the conjunctiva is exposed to an environmental allergen and binds to specific IgE on the conjunctival mast cells.¹¹ This immediate response lasts clinically for 20 to 30 minutes.¹⁴ This causes enhanced tear

levels of histamine, tryptase, prostaglandins, and leukotrienes.¹⁴ Mast cell degranulation induces activation of vascular endothelial cells and other cellular responses, which lead to the recruitment phase of inflammation. This leads to the late phase, which corresponds to the clinical inflammation characterized by the ocular signs and symptoms of allergic conjunctivitis.¹⁴

Treatment of VKC requires a multilevel approach that includes patient education, environmental strategies, pharmacologic and sometimes surgical intervention. When children are involved, parents must be educated about the nature of the condition, its possible duration, and potential complications of the disease.⁵ Practitioners should stress the chronic, recurrent, and resolving nature of the condition.⁴ In addition, environmental strategies can involve removing the offending agent, changing climate, or avoiding triggers, such as sun, wind, or salt water.^{3,8} Because changing climate, such as moving to a different location may be difficult, an easier lifestyle modification can be the frequent use of sunglasses, hats with visors, or swimming goggles.⁵ Other options can include avoiding parks, especially during the warmest hours, not playing with flowers or plants, and frequent hygiene such as hand, face, and hair washing.^{4,5} The use of cold compresses and nonpreserved artificial tears also can offer relief and dilute the allergen on the ocular surface.^{4,17}

There are several pharmacologic treatment options for VKC, including topical therapies. Treatment choice depends upon the severity of the disease process. Initial therapy can include mast-cell stabilizers. Among these, cromolyn sodium, lodoxamide and nedocromil sodium (Alocril) are used early and should be used continuously throughout the season to reduce signs and symptoms.⁵ These drugs require a loading period in which they must be applied before exposure to the antigen. Thus, compliance could be an issue because patients may find it difficult to adhere to a strict and frequent dosing regimen before experiencing an allergic reaction. Also, their slow initial onset of action makes them a less ideal first drug of choice.¹⁷

In addition, antihistamines such as levocabastine hydrochloride, are effec-

tive in relieving ocular inflammation and itching. However, they necessitate frequent dosing of up to four times daily due to their limited duration of action. This frequent dosing could decrease compliance.¹⁷

Decongestants, such as oxymetazoline hydrochloride, tetrahydrozoline hydrochloride and naphazoline hydrochloride, are easily found over-the-counter. They can have adverse effects, however, including burning and stinging upon instillation, mydriasis, and rebound hyperemia with chronic use. They act primarily as vasoconstrictors to relieve erythema.¹⁷

Other candidates for treatment include nonsteroidal anti-inflammatory drugs (NSAIDs). An example is ketorolac tromethamine, which works on the arachidonic acid cascade and is effective in relieving ocular itching.¹⁷ Like decongestants, NSAIDs can cause discomfort on instillation and, hence, may affect patient compliance.¹⁷ Although the long-term effects of intraocular pressure, wound healing, and corneal tissue remain unknown, NSAIDs have a good safety profile compared to topical steroids.³

Antihistamines with mast-cell stabilizing properties, such as olopatadine and ketotifen, may also be used to relieve mild to moderate forms of VKC.⁵ These drugs have a dual mode of action because they inhibit mast-cell degranulation while competitively blocking histamine binding to histamine 1 (H1) receptors. This allows them to have a rapid mode of action and thus can allow for greater compliance over the pure mast-cell stabilizers.¹⁷

Moderate to severe VKC should be treated with topical steroids because of their greater efficacy. However, because they can raise intraocular pressure and cause cataracts with prolonged use, steroid usage should be strictly monitored with frequent follow-up visits. For instance, there is a 2% incidence of glaucoma in VKC patients.⁷ Various steroids used and recommended include: loteprednol, prednisolone acetate, prednisolone sodium phosphate, fluorometholone, and rimexolone. Of these, only loteprednol is specifically approved for ocular seasonal allergic conjunctivitis. Dosing for topical ste-

roids varies depending upon the severity of the disease and can range from four times daily to once daily.⁹

An alternative to topical steroids for severe forms of VKC is cyclosporine A (CsA) from 0.5% to 2% ophthalmic emulsions.^{5,8} Insoluble in water, cyclosporine is administered by oily bases such as olive oil or castor oil.^{5,8,18,19} This can cause intolerable symptoms that range from burning to blurry vision.^{5,18} Dosing starts at four times daily and can be reduced to once daily as the disease process subsides.^{5,7,8,18} Cyclosporine works by blocking Th2 lymphocyte proliferation and interleukin production, as well as by inhibiting histamine release and eosinophil recruitment within the conjunctiva.⁸ In essence, it acts as an immunomodulator.¹⁸ A study showed a significant reduction in signs, symptoms, and tear levels of eosinophil cation protein in VKC patients after 2 weeks of using CsA four times daily.⁵ An example of topical cyclosporine A is Restasis.^{7,19} The advantage of this treatment over topical steroids is that it does not cause an increase in intraocular pressure.^{5,18,19} The disadvantage is the high cost of topical CsA treatment. A study found that topical CsA 0.05% had a beneficial effect in patients with VKC who were not responding to treatment from steroids, antihistamines, and mast-cell stabilizers.¹⁹

Oral medication can be used to reduce symptoms of ocular allergy associated with VKC. Oral antihistamines, such as loratadine (Claritin), can be used to reduce symptoms of nasal and ocular allergy symptoms, but it has little effect on VKC.⁸ For instance, loratadine has been shown to have a protective effect in conjunctival provocation studies.¹⁷ Also, oral NSAIDs, such as aspirin, have been shown effective in reducing signs and symptoms of VKC.⁸ Studies have shown that low levels of aspirin therapy at dosages of 0.5-1 g/day administered systemically are beneficial for VKC patients.⁵ Because many patients are children, however, one needs to be cautious, as frequent use of aspirin poses its own risks.⁵

Surgical intervention can sometimes be warranted in the later stages. Physical removal of corneal plaques is recommended to allow for corneal re-epithelization and to allow for reduction

of symptoms such as photophobia, pain, and irritation.⁵ Recently, amniotic membranes have been used in the treatment of corneal ulcers in VKC patients. Giant papillae excision is used for mechanical pseudoptosis and for gross papillary formations.⁵ Cryotherapy of the tarsal mucosa may be performed, but this is not recommended because of potential scarring, no immunosuppressant effects, and the inability to always resolve signs and symptoms.⁵ For severe forms of VKC, oral mucosal grafting and saphenous vein transplantation may be used, but these procedures are invasive and can permanently change the anatomy and physiology of the lid.⁵

What are the pharmacological actions of some of the commonly used drugs in the treatment of VKC? Because mast cell degranulation is a central event in VKC and causes many of the symptoms and signs, medications such as mast-cell stabilizers help to prevent the degranulation of the mast cells and the release of histamine. For instance, the prototypical mast-cell stabilizer, cromolyn sodium, can be used long-term without side effects, but it can take many days to reach therapeutic levels.⁴ Antihistamines, such as emadastine and levocabastine, are topical selective H1 blockers that work by blocking the histamine receptors and causing a downregulation of chemicals and, hence, limiting chemotaxis of inflammatory cells.⁴ The newer generation antihistamines, olopatadine and ketotifen, are H1 receptor antagonists that have mast-cell stabilizing properties that make them suitable for twice-a-day dosing.⁴ Nonsteroidal anti-inflammatory drugs, such as ketorolac and diclofenac, help to relieve ocular pruritis and conjunctival hyperemia by inhibiting the synthesis of prostaglandins.⁴ Topical steroids, which target both legs of the anti-inflammatory cascade, are effective in controlling the signs and symptoms of VKC, but they should not be used long-term because of their potential to cause side effects, such as cataracts, glaucoma, and increased susceptibility to viral and fungal infections.⁴

VKC generally has a positive visual outcome. In most patients, it spontaneously resolves after puberty and leaves no serious visual complications.⁷ However, it can be chronic and visually dev-

astating. Among the most severe visual consequences of the disease are corneal shield ulcers, which develop in 3% to 11% of VKC patients.⁷ A reduction of best-corrected visual acuity from corneal scarring occurs in approximately 6% of cases.⁷ There is also a 2% incidence of glaucoma from long-term steroid use in VKC patients.⁷ In the most severe cases, VKC can be resistant to medical treatment and surgery (such as resection of giant papillae of the upper eyelid.)

Although the exact etiology of VKC is unclear, it appears to have a multifactorial origin.^{5,7} In the past, VKC was considered a type 1, IgE-mediated disorder.^{7,10} Recent clinical observations suggest it is a Th2-driven mechanism similar to that of asthma. A cascade effect of mast cells and basophils causes histamine release and ensuing inflammatory lymphocytes and eosinophils that lead to ocular surface inflammation and tissue damage.¹⁰ For example, numerous degranulated eosinophils are evident in conjunctival scrapings, tear fluid, and ocular discharge of VKC patients.¹⁰ The resulting vernal papillae are caused by infiltration of lymphocytes and plasma cells on the upper tarsal plate.⁷ Other studies suggest neural and endocrine factors. For instance, neuropeptides have been found in the tears and serum of patients with VKC.⁸ Yet other research has shown that certain sex hormones, such as estrogen and progesterone, are overexpressed in the conjunctiva of patients with VKC.^{7,8} This might be demonstrated by the greater frequency of men versus women with VKC.^{5,7}

This case illustrates several key concepts and goals in clinical care. The astute clinician must take a careful case history and be reminded of important patient demographics, such as age, sex, and race. Since VKC can mimic several other clinical entities, a list of differential diagnoses should be kept at hand so that it can be altered as treatment progresses. Recognizing hallmark signs is crucial to making a correct and swift diagnosis. In addition, taking a careful case history also involves probing for potential allergens that could be triggers for the condition. The history in this case included the boy's positive medical history of allergies and asthma in addition to the acquisition of a cat to

his home, which may have been a contributing factor.

In addition to thoroughly understanding a patient's background, patient and parental education regarding the condition and treatment options is crucial. The mother and the patient were frustrated in the earlier stages of treatment because the erythromycin, olopatadine, and ketotifen did not initially relieve symptoms. Close and frequent follow-up visits were essential in this case to monitor compliance, as well as watch for any changes in signs and symptoms. As demonstrated, patient education is a significant component of care because poor understanding or inadequate patient education can lead to misuse of medication, frustration, and, eventually, noncompliance.

In this case, the signs were mild in the early stages but progressed and eventually revealed hallmark signs, such as limbal Horner-Trantas dots. It is important for the clinician to exercise flexibility in clinical diagnosis and treatment throughout the care of the patient. Initial diagnosis in this case was different from the final diagnosis. Early treatment with erythromycin, olopatadine, and ketotifen did not significantly relieve symptoms and, therefore, had to be modified. Although one does not know if this was a result of the mother's discontinuing the child's medication before it had sufficient time to reach therapeutic levels or if it was the result of inadequate treatment at the time. Even though the mother was educated regarding the length of time for the medication to achieve therapeutic level and for the condition to resolve, she did not adhere to the recommendation. One can see that noncompliance regarding medication instillation and recommended follow-up is common in clinical care. Fortunately, this case of VKC was moderate and did not lead to a corneal shield ulcer or other complications. As a result, alternative treatments, such as stronger steroids, oral medications, and surgical intervention were not necessary. It was interesting to note that the patient fit the stereotypical VKC patient who has a personal history of allergies, such as eczema, asthma, and seasonal allergies.

Conclusion

This case demonstrates the role of patient history and close clinical observation in the diagnosis of VKC. Early treatment is important to reduce the risk of further damage to the cornea. Because signs and symptoms may change presentation, it is important to reevaluate diagnosis and treatment. In most cases, a combination of epidemiology symptoms and hallmark signs confirm the disease. Clinicians must educate parents on the potential chronic nature of the condition, as well as appropriate follow-up care. For recurrent cases, parents can bring their children for preventative eye drops such as cromolyn sodium prior to the allergy season. Resolved cases of VKC should be followed annually to monitor for recurrence. With the proper diagnosis, treatment, and patient education, VKC usually has a good visual outcome. Hopefully, future research will be geared toward finding safer and more effective drug alternatives. Gene therapy, which seeks to understand the genetic characteristics and risk factors for VKC patients, may help shed light on new treatment strategies for VKC.

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References

1. Ocular Immunology and Uveitis Foundation website, Ocular Allergy, March 2005. Available from: <http://www.uveitis.org/medical/articles/case/Allergy.html>; accessed May 7, 2010.
2. Kanski J. *Clinical Ophthalmology 4th Ed.* Oxford: Butterworth-Heinemann; 1999; 66-78.
3. Swamy BN, Chilov M, McClellan K, Petsoglou C. Topical non-steroidal anti-inflammatory drugs in allergic conjunctivitis: meta-analysis of randomized trial data. *Ophthalmic Epidemiol.* 2007;14:311-319.
4. Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol.* 2009;87:133-147.
5. Leonardi A. Vernal keratoconjunctivitis: pathogenesis and treatment. *Prog Retin Eye Res.* 2002;21:319-339.
6. Kaiser P, Friedman N, Pineda R. *The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology 2nd Ed.* Philadelphia: Saunders;2004; 124-126.
7. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, et al. Vernal keratoconjunctivitis revisited: A case series of 195 patients with long-term followup. *Ophthalmology.* 2000;107:1157-1163.
8. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. *Eye.* 2004;18:345-351.
9. Sowka J, Gurwood A, Kabat A. Vernal keratoconjunctivitis. *The handbook of ocular disease management.* March 2007:11A-14A.
10. Mantelli F, Santos M S, Petitti T, Sgrulletta R, Cortes M, Lambiase A, et al. Systematic review and meta-analysis of randomized clinical trials on topical treatments for vernal keratoconjunctivitis. *Br J Ophthalmol.* 2007;91:1656-1661.
11. Kumagai N, Fukuda K, Fujitsu Y, Yamamoto K, Nishida T. Role of structural cells of the cornea and conjunctiva in the pathogenesis of vernal keratoconjunctivitis. *Prog Retin Eye Res.* 2005;25:165-187.
12. Reinhard T, Larkin D. *Corneal and External Eye Disease.* Berlin: Springer;2006.
13. Jeng B, Whitcher J, Margolis T. Pseudogerontoxon. *Clin Experiment Ophthalmol.* 2004;32:433-434.
14. Leonardi A, Motterle L, Bortolotti M. Allergy and the eye. *Clin Experiment Immunol.* 2008;53(suppl 1):17-21.
15. Sowka J, Gurwood A, Kabat A. Superior limbic keratoconjunctivitis. *The handbook of ocular disease management.* March 2007:12A-15A.
16. Sowka J, Gurwood, A, Kabat A. Atopic keratoconjunctivitis. *The handbook of ocular disease management.* April 2008:16A-18A.
17. Bielory L, Katelaris CH, Lightman S, Naclerio RM. Treating the ocular component of allergic rhinoconjunctivitis and related eye disorders. *MedGenMed.* 2007;9:35.
18. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J, et al. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther.* 2009;25:365-372.
19. Ozcan AA, Ersoz TR, Dulger E. Management of severe allergic conjunctivitis with topical cyclosporine A 0.05% eyedrops. *Cornea.* 2007;26:1035-1038.