Allergic Ocular Diseases

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Abstract

The ocular surface may exhibit a wide variety of immunologic responses resulting in inflammation of the conjunctiva and cornea. Diagnosis of allergic conjunctivitis is generally made by thorough history and careful clinical observation. The presence of an antigen triggers the allergic cascade, and, thus, avoidance of the offending antigen is the primary behavioral modification for all types of allergic conjunctivitis (Takamura et al., Allergol Int 66:220–229,

2017; Takamura, J Jpn Ophthalmol Soc 114:831–870, 2010). In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective symptoms and objective findings accompanying allergic inflammation (Singh et al., J Allergy Clin Immunol 126:778–783, 2010).

Keywords

Allergic conjunctivitis · Atopic keratoconjunctivitis (AKC) · Giant papillary conjunctivitis (GPC) · Perennial allergic conjunctivitis (PAC) · Seasonal allergic conjunctivitis (SAC) · Vernal keratoconjunctivitis (VKC)

4.1 Introduction

Allergic conjunctival disease is defined as "a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective symptoms and objective findings." The traditional classification for hypersensitivity reactions is that of Gell and Coombs and is currently the most commonly known classification system (Table 1). Conjunctivitis associated with type I allergic reaction is considered allergic conjunctival disease even if other types of inflammatory reactions are involved (Takamura et al. 2017; Takamura 2010). The most common causes of allergic conjunctivitis are seasonal allergens such as pollen and mold spores. People with seasonal allergic rhinitis (hay fever) normally notice their symptoms worsen when they go outdoors on days with high pollen counts. Indoor allergens such as dust mites and pet dander can also cause eye allergies year-round. If you suffer from this type of allergy, you may notice your symptoms worsen during certain activities such as cleaning your house or grooming a pet. The commoner conditions are mild and do not affect the cornea. The rare diseases involve the cornea and can be sight-threatening. Allergic conjunctivitis is a very common condition that occurs with allergic rhinitis and contributes to burden of disease and QOL.

Table 1 Gell and Coombs classification system for various immunologic hypersensitivity reactions (Singh et al. 2010)

Type I: Anaphylaxis type (or immediate type) reactions
Immediate hypersensitivity reactions occur when a sensitized individual comes in contact with a specific antigen. Immunoglobulin E (IgE) has a strong affinity for mast cells, and the cross-linking of two adjacent IgE molecules by the antigen triggers mast cell degranulation. The mast cell's degranulation releases various preformed and newly formed mediators of the inflammatory cascade
Type II: Antibody-mediated cytotoxic type reactions
It is this type of reaction that autoantibodies bind to self-tissues and complements activated by the binding of autoantibodies injury their tissues
Type III: Immune complex-mediated type reactions
Hypersensitivity reactions result in antigen-antibody immune complexes, which deposit in tissues and cause inflammation. A classic systemic type III reaction is the Arthus reaction, and ocular type III hypersensitivity reactions include Stevens–Johnson syndrome and marginal infiltrates of the cornea. These type III reactions can often induce a corneal immune (Wessely) ring that disintegrates as the inflammatory reaction subsides
Type IV: Delayed type reactions
Hypersensitivity reactions, also known as cell-mediated immunity, are interceded by T lymphocytes. This inflammatory cell-driven reaction is also referred to as delayed-type hypersensitivity, since its onset is generally after 48 h, in contrast to the type I reaction, which is an immediate hypersensitivity. Also, type IV hypersensitivity reactions imply immunocompetence on the part of the individual since an intact immune system is required to mount the cell-mediated response. Ocular examples of type IV hypersensitivity include phlyctenular keratoconjunctivitis, corneal allograft rejection, contact dermatitis, and drug allergies
Type V: Stimulating antibody type reactions
Additional type that is sometimes (especially in the UK) used as a distinction from type II. It is a feature of this reaction that autoantibody binds but does not involve tissue damage. Instead of binding to cell surfaces, the antibodies recognize and bind to the cell surface receptors, which either prevents the intended ligand binding with the receptor or mimics the effects of the ligand, thus impairing cell signaling. These conditions are more frequently classified as type II, though sometimes they are specifically segregated into their own subcategory of type II

4.2 Classification

Allergic conjunctival disease is classified into multiple disease types according to the presence or absence of proliferative changes, complicated atopic dermatitis, and mechanical irritation by foreign body. Allergic conjunctivitis may be divided into five major subcategories: (i) Allergic conjunctivitis without proliferative change. Allergic conjunctivitis is subdivided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) according to the period of onset of the symptoms. Whereas symptoms of SAC are occurring during one season, symptoms of PAC are occurring throughout all seasons (Singh et al. 2010); (ii) Atopic keratoconjunctivitis (AKC), complicated with atopic dermatitis (Hogan 1953; Chen et al. 2014); (iii) Vernal keratoconjunctivitis (VKC) with proliferative changes (Kumar 2009); and (iv) Giant papillary conjunctivitis (GPC) induced by irritation of a foreign body (Allansmith et al. 1977; Aswad et al. 1988). Allergic conjunctival diseases are also classified in Table 2.

4.2.1 SAC and PAC

Allergic conjunctival diseases without proliferative changes in the conjunctiva include SAC where symptoms appear in a seasonal manner and PAC where symptoms persist throughout the year. These are commonly grouped together. These common IgE-mediated diseases are related to seasonal or perennial allergens. They are characterized by symptoms of ocular itching, watering and redness, and signs of hyperemia and edema of the tarsal conjunctival surfaces. There is frequently an association with allergic rhinitis. SAC is intermittent in nature, and in temperate regions, follows exposure to pollen allergens in sensitized individuals. PAC is a mild, persistent form of allergic conjunctivitis resulting from continuing exposure to persistent allergens such as house dust mites. Allergic rhinitis is often accompanied by multiple ocular symptoms. There is an increase in the frequency of symptoms in those younger than 50 years in the populations of subjects with ocular and nasal symptoms combined and isolated nasal symptoms ($P < 0.001$) (Singh et al. 2010). Ocular symptoms are more frequent than nasal symptoms in relation to animals ($P < 0.001$), household dust ($P < 0.001$), and pollen ($P < 0.001$).

Table 2 Classification of allergic conjunctival diseases

Allergic conjunctivitis without involvement of the cornea (Singh et al. 2010)
(i) Seasonal allergic conjunctivitis (SAC)
(ii) Perennial allergic conjunctivitis (PAC)
Upper palpebral conjunctival with involvement of the cornea
(iii) Atopic keratoconjunctivitis (AKC) (Hogan 1953; Chen et al. 2014)
(iv) Vernal keratoconjunctivitis (VKC) (Kumar 2009)
Papillary conjunctivitis induced by irritation of a foreign body
(v) Giant papillary conjunctivitis (GPC) (Allansmith et al. 1977; Aswad et al. 1988)

4.2.2 AKC

This is a severe disease which is associated with atopic dermatitis. The condition is lifelong, starting in the third of fourth decade (Fig. 1). AKC is a chronic allergic conjunctival disease that may occur in patients with facial atopic dermatitis. In 1952, Hogan described this disease as a bilateral conjunctivitis occurring in five male patients with atopic dermatitis (Hogan 1953). Originally

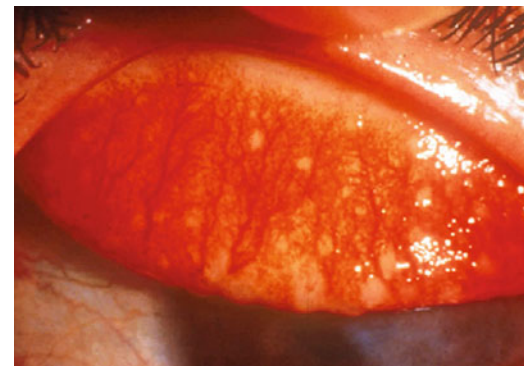

Fig. 1 Atopic keratoconjunctivitis (AKC). Upper palpebral conjunctival findings in AKC. Hyperemia, opacity, and subconjunctival fibrosis are present. Giant papillae may be present although many AKC cases have no proliferative changes

reported to flare with worsening dermatitis, atopic keratoconjunctivitis in some patients evolves independent of dermatitis (Chen et al. 2014). Atopy affects 5–20% of the general population. Atopic keratoconjunctivitis not only occurs in 20–40% of individuals with atopic dermatitis but it is also associated with a 95% prevalence of concomitant eczema and an 87% prevalence of asthma. This condition is more prevalent in men than in women, and the peak age of incidence is in persons aged 30–50 years (range, late teens to 50 years). Giant papillae may be present although many AKC cases have no proliferative changes. Upper palpebral conjunctival findings in AKC. Hyperemia, opacity, and subconjunctival fibrosis are present. IgE-mediated mechanisms may be implicated. The symptoms are perpetual ocular itching, soreness, impaired vision, and a sensation of dryness. Signs include chronic lid margin infection, chronic cicatrizing conjunctivitis, eczema of the eyelids, tear abnormality, and progressive scarring and vascularization of the cornea.

4.2.3 VKC

This is a severe inflammatory disease which may be intermittent or, less frequently, persistent (Fig. 2). VKC is, in about 60% of cases, associated with IgE-dependent hypersensitivity (Allansmith et al. 1977). Many VKC cases accompany atopic dermatitis, and atopic conditions of the external ocular surface. It characteristically affects young males in hot dry climates in a seasonal manner; however, this is not always the rule. VKC is characterized by conjunctival proliferative changes such as papillary hyperplasia of the palpebral conjunctiva or its enlargement, and swelling or limbal gelatinous hyperplasia. The symptoms are ocular watering, stickiness, itching, and difficulty with opening the eyes on awaking. If the cornea is involved, pain, blurred vision, and photophobia are experienced. The signs are giant papillary hyperplasia of the upper tarsal conjunctival surfaces, erosion of the corneal epithelium, and inflammation at the limbus. Corneal lesions with various severities including superficial punctate keratitis, corneal erosion, persistent corneal epithelial defect, corneal ulcers, or corneal plaque have been observed in VKC. Upper palpebral conjunctival findings in VKC. Conjunctival hyperemia, conjunctival edema, eye discharge, and formation of giant papillae are present.

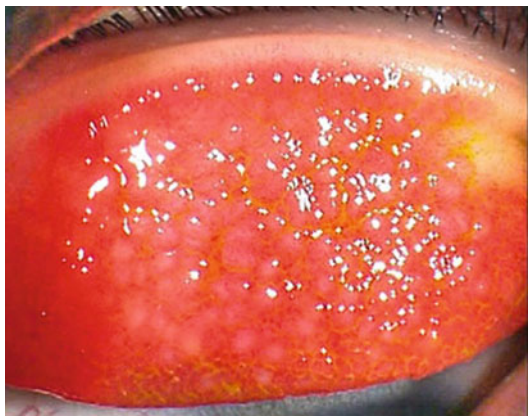

Fig. 2 Vernal keratoconjunctivitis (VKC). Upper palpebral conjunctival findings in VKC. Conjunctival hyperemia, conjunctival edema, eye discharge, formation of giant papillae are present

4.2.4 GPC

This is not a true ocular allergy but rather an repetitive mechanical irritation, often in due to contact lenses, that is aggravated by concomitant allergy (Fig. 3). This disease, also known as foreign body associated papillary conjunctivitis, results from trauma caused by contact lens edges, ocular protheses, or postoperative sutures. It may also evolve from spontaneous lid eversion resulting in conjunctival rubbing against the pillow, the so-called floppy eyelid syndrome. Upper subtarsal papillae, not always giant in size (> 1 mm), is the hallmark sign of the disease. GPC is conjunctivitis that accompanies proliferative changes in the upper palpebral conjunctiva induced by mechanical irritations such as contact lenses, ocular prosthesis, or surgical sutures. Contact lenses have become so familiar that both patients and physicians are likely to think of them as innocuous objects. They are widely prescribed for cosmetic reasons as well as to correct a variety of conditions that impair sight. But even the best tolerated contact lens is a prosthetic device on the surface of the eye and, like all

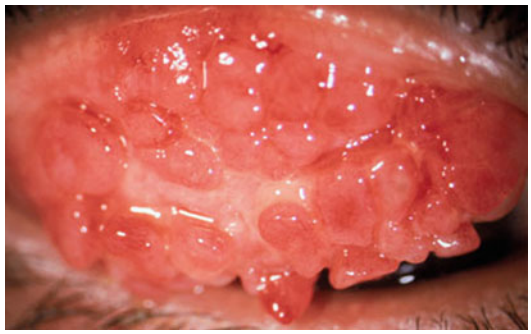

Fig. 3 Giant papillary conjunctivitis (GPC). Upper palpebral conjunctival findings in GPC. Hyperemia and dome-like giant papillae are present

prostheses, is foreign to the body. The tissues of the eye and its adnexa therefore mobilize normal responses to foreign bodies. For many contact lens wearers, the result may be minor inconvenience and relatively inconsequential problems with lens tolerance. For others, however, erythema, itching, increased mucus production, and formation of giant papillae on the upper tarsal conjunctiva may make prolonged wearing of contact lenses impossible. This disease related to wearing contact lenses and other ocular prostheses is now recognized as GPC. Hyperemia and dome-like giant papillae are present. Patients who develop GPC secondary to their wearing contact lenses for purely cosmetic reasons could, albeit reluctantly, change from contact lenses to wearing eyeglasses. But the proper care of patients who must wear contact lenses (e.g., in the event of keratoconus of high myopia) requires a range of hygienic and medical interventions to manage the possible adverse reactions to wearing contact lenses and to prevent the onset of GPC. There is no evidence that generally IgE-sensitized individuals are at greater risk of developing the disease. The cornea is rarely involved.

4.3 Causes

4.3.1 SAC

Seasonal, intermittent, allergic conjunctivitis is triggered by the same allergens responsible for intermittent allergic rhinitis. In the Northern Hemisphere these are tree pollens in April/May, grass pollens in June/July, and mold spores and weed pollens in July/August.

4.3.2 PAC

Perennial, persistent, allergic conjunctivitis is triggered by house dust mites, molds, and animal allergens, which may be present year round, although the symptoms do show some seasonal variation.

4.3.3 VKC

The majority of cases of VKC are intermittent and can occur during the high pollen season, although persistent cases do occur in warm subtropical or desert climates. Published reports of the association with IgE-mediated atopic disease vary between 15% and 60%. While there is a relationship between the condition and positive skin tests, the relationship is not necessarily causal.

4.3.4 AKC

AKC is a perennial disease which, when associated with the IgE-mediated subgroup of atopic eczema, may be exacerbated by contact with specific allergens such as house dust mites, mold spores, animal danders, and rarely foods.

4.3.5 GPC

Giant papillary conjunctivitis occurs in the presence of foreign bodies in the eye, such as contact lenses or ocular prostheses. Papillae develop on the upper tarsal conjunctiva along the line of contact with the source of mechanical trauma, e.g., the lens edge. The upper eyelid may be traumatized with each blink of the eye, which occurs between 10,000 and 12,000 times daily, and the area of trauma may serve as an entrance for antigen possibly derived from altered proteins or chemicals in contact lens solutions, although no

single causative allergen has been identified in this condition to date.

4.4 Epidemiology

Allergic conjunctivitis occurs very frequently and is seen most commonly in areas with high seasonal allergen and pollen counts. Allergic conjunctivitis is one of the most common forms of conjunctivitis. In a report from the National Health and Nutrition Examination Survey studying the epidemiology of allergic conjunctivitis, 6.4% and 29.7% of 20,010 patients reported ocular symptoms and combined ocular and nasal symptoms, respectively. Forty percentage of the population reported experiencing at least one occurrence of ocular symptoms in the past 12 months (Singh et al. 2010). On the other hand, in Japan, the proportion of persons with allergic conjunctival diseases diagnosed by ophthalmologists was 12.2% in children and 14.8% in adults. From these results, the proportion of persons with allergic conjunctival diseases in the entire population is estimated to be about 15–20%. A research group on allergic ocular disease of the Japan Ophthalmologists Association conducted epidemiologic surveys of all patients with allergic conjunctival diseases that were treated at 28 facilities (7 university attached hospitals, 5 general hospitals, and 16 ophthalmic hospitals and clinics) all over Japan during the period from January 1, 1993 to December 31, 1995 (Takamura et al. 2017). They found that female patients with SAC or PAC outnumbered male patients by 2:1, whereas male patients with VKC outnumbered female patients by 2:1. The number of patients with allergic conjunctive disease was maximum at the age of 10 and the incidence decreased with aging. The main subjective symptoms were an ocular itching, ocular hyperemia, eye discharge, and a foreign body sensation in each disease type. In SAC, symptoms of allergic rhinitis such as sneezing, rhinorrhea, nasal blockade were found in many cases.

AKC is a relatively uncommon but potentially blinding ocular condition. It occurs predominantly between the late teenage years and fifth decade of life. In 1953, Hogan described this disease as a bilateral conjunctivitis occurring in five male patients with atopic dermatitis (Hogan 1953). Originally reported to flare with worsening dermatitis, atopic keratoconjunctivitis in some patients evolves independent of dermatitis (Kumar 2009). Atopy affects 5–20% of the general population. Atopic keratoconjunctivitis not only occurs in 20–40% of individuals with atopic dermatitis but it is also associated with a 95% prevalence of concomitant eczema and an 87% prevalence of asthma. This condition is more prevalent in men than in women, and the peak age of incidence is in persons aged 30–50 years (range, late teens to 50 years). Other than atopic keratoconjunctivitis, common ocular atopic phenomena include allergic conjunctivitis, giant papillary conjunctivitis, and vernal keratoconjunctivitis.

VKC occurs predominantly in areas with tropical and temperate climates, such as the Mediterranean, the Middle East, and Africa. The limbal form of VKC commonly occurs in dark-skinned individuals from Africa and India. Also, VKC has a significant male preponderance, typically affecting young males. The onset of VKC generally occurs in the first decade and persists throughout the first two decades. Symptoms usually peak prior to the onset of puberty and then subside.

4.5 Pathophysiology

The pathological conditions of allergic conjunctival disease with lesions in the conjunctiva are assumed to be caused by interactions between various immune system cells and resident cells, which are mediated by physiologically active substances (e.g., histamine and leukotriene), cytokines, and chemokines. Eosinophils are the main effector cells in allergic conjunctival disease. Various cytotoxic proteins released from eosinophils infiltrating locally into the conjunctiva are thought to cause keratoconjunctival disorders such as severe AKC and VKC. It is also speculated that keratoconjunctival resident cells may be involved in the etiology of allergic conjunctival disease by

cytokine-stimulated production of chemokines such as eotaxin and thymus and activation-regulated chemokine (TARC) which cause eosinophil and Th2 cell migrations from the circulation, respectively.

4.5.1 SAC and PAC

The general idea is that there is an allergic response in the conjunctivitis to an allergen. The allergen causes cross-linkage of membrane-bound IgE that causes mast cells to degranulate. This causes a release and cascade of allergic and inflammatory mediators, such as histamine. Since the conjunctiva is a mucosal surface similar to the nasal mucosa, the same allergens that trigger allergic rhinitis may be involved in the pathogenesis of allergic conjunctivitis. Common airborne antigens, including dust, molds, pollen, grass, and weeds, may provoke the symptoms of acute allergic conjunctivitis, such as ocular itching, redness, burning, and tearing. The main distinction between SAC and PAC, as implied by the names, is the timing of symptoms. Individuals with SAC typically have symptoms of acute allergic conjunctivitis for a defined period of time, that is, in spring, when the predominant airborne allergen is tree pollen; in summer, when the predominant allergen is grass pollen; or in fall, when the predominant allergen is weed pollen. Typically, persons with SAC are symptom-free during the winter months in cooler climates because of the decreased airborne transmission of these allergens. Seasonal allergic conjunctivitis can manifest itself through tear film instability and symptoms of eye discomfort during the pollen season. One study found that outside the pollen season, allergic inflammation did not cause permanent tear film instability. In contrast, individuals with PAC may have symptoms that last the year round; thus, PAC may not be caused exclusively by seasonal allergens, although they may play a role. Other common household allergens, such as dust mite, cockroach dust, cigarette smoke, airborne allergens, molds, and pet dander, may be responsible for the symptoms of PAC.

4.5.2 VKC

VKC is a chronic bilateral inflammation of the conjunctiva, commonly associated with a personal and/or family history of atopic diseases. More than 90% of patients with VKC exhibit one or more atopic conditions, such as asthma, eczema, or seasonal allergic rhinitis. Corneal complications and conjunctival scarring frequently occur, particularly in more severe cases and in patients whose VKC onsets at a very young age. A personal or family history of atopy is seen in a large proportion of VKC patients. VKC was originally thought to be due to a solely IgE-mediated reaction via mast cell release. It has now been shown that IgE is not enough to cause the varied inflammatory response that is seen with VKC. Activated eosinophils are thought to play a significant role and these can be shown consistently in conjunctival scrapings; however, mononuclear cells and neutrophils are also seen. Additional attention has been given to the CD4 T-helper-2 driven type IV hypersensitivity with immunomodulators such as IL-4, IL-5, and basic fibroblast growth factor (bFGF). Thought has been given to a possible endocrine method as well as there is a decrease in symptoms and prevalence after puberty. A hereditary association has been suggested, but no direct genetic associations have been made. VKC is seen more often in patients who have atopic family histories, but no clear correlation with specific genetic loci has been elucidated (Kumar 2009).

4.5.3 AKC

The pathophysiological mechanism of disease is not fully understood. However, evidence suggest the involvement of various cells within the conjunctiva, specifically eosinophils, fibroblasts, epithelial cells, mast cells, and TH2 lymphocytes. Allergens activate these various cells creating an inflammatory response. AKC is a bilateral inflammation of conjunctiva and eyelids, which has a strong association with atopic dermatitis. It is also a type I hypersensitivity disorder with many similarities to VKC, yet AKC is distinct in a number

of ways. In 1953, Hogan first described the association between atopic dermatitis and conjunctival inflammation (Hogan 1953). He reported five cases of conjunctival inflammation in male patients with atopic dermatitis. Atopic dermatitis is a common hereditary disorder that usually first appears childhood; symptoms may regress with advancing age. Approximately 3% of the population is afflicted with atopic dermatitis, and, of these, approximately 25% have ocular involvement (Chen et al. 2014). Again, more advanced cases may result in significant conjunctival cicatrization, severe dry eye, and loss of corneal clarity through chronic or acute keratitis.

4.5.4 GPC

Because GPC is a common complication of contact lens wear, it has been called contact lens-induced papillary conjunctivitis. Spring first described giant papillary conjunctivitis in association with contact lens use, which is hypersensitivity-related inflammation of the ocular tarsal palpebral conjunctivae (Aswad et al. 1988). Prior to the popularization of hydrogel (soft) contact lenses over the past four decades, such reactions were primarily seen as immunoglobulin E (IgE)-mediated ocular allergies: allergic conjunctivitis or VKC, which occasionally becomes severe and leads to shield corneal ulcers and other complications. However, GPC related to contact lens wear never leads to the severe tissue morbidity of VKC. Giant papillary conjunctivitis symptoms and signs, such as papillary changes in the tarsal conjunctiva, have been associated with the use of all types of contact lenses (e.g., rigid, hydrogel, silicone hydrogel, piggyback, scleral, prosthetic) (Henriquez et al. 1981). A combination of type I and type IV hypersensitivity reactions may be responsible for the pathogenesis of GPC (Allansmith et al. 1977). The immediate hypersensitivity is mediated by specific IgE bound to mast cells in the conjunctival, but the nature of the specific antigen or antigens has not been discovered. The delayed inflammatory reaction is mediated by sensitized lymphocytes, reacting with antigen to release lymphokines, with resultant tissue inflammation and tissue damage. Cellular infiltration of the conjunctival epithelium with mast cells, eosinophils, basophils, and polmorphonuclear leukocytes, as well as an occasional lymphocyte, is regularly observed in GPC. Eosinophils are present in conjunctival scrapings in somewhat less than one-fourth of individuals with GPC. The involvement of mast cells, basophils, or eosinophils in abnormal positions in the conjunctival tissue reflects the disturbed nature of the immune apparatus in GPC. All GPC patients examined had one of the following abnormalities: mast cells in the epithelium, eosinophils in the epithelium or substantia propria, or basophils in the epithelium or substantia propria. It is believed that an antigen is present, in predisposed individuals, which stimulates the immunological reaction and the development of GPC. Prolonged mechanical irritation to the superior tarsal conjunctiva, of the upper lid, from any of a variety of foreign bodies may also be a contributing factor in GPC. Although contact lenses (hard and soft) are the most common irritant, ocular prostheses, extruded scleral buckles, elevated glaucoma shunts or filtering blebs, scleral shells, and exposed sutures following previous surgical intervention may also precipitate GPC.

4.6 Subjective

In seasonal and perennial allergic conjunctivitis, important features of the history include a personal or family history of atopic disease, such as allergic rhinitis, bronchial asthma, and/or atopic dermatitis. The most important feature in the clinical history is the symptom of itching, because even if tissue damage due to allergic inflammation is relatively mild, ocular injury can be large due to mechanical tissue destruction due to ocular scratching the eyes. Although anyone can endure the itching of the eyeball or eyelid while getting up, since everyone may unconsciously scratches the eyes against the itching without hesitation while sleeping, the patient education is necessary for prevention.

Without itching, the diagnosis of allergic conjunctivitis becomes suspect. Itching is the most

characteristic symptoms in allergic conjunctival disease, but some patients complain of a foreign body sensation instead. The foreign body sensation is frequently present in allergic conjunctival disease. Aside from cases where slight itching is felt as a foreign body sensation, it is very likely that when many conjunctival papillae sweep the cornea at the time of blinking, a foreign body sensation may occur. In allergic conjunctival disease, lymphocytes and eosinophils account for the majority of inflammatory cells, while neutrophils are few, serous and mucous discharge is often present, and the nature of the discharge differs from the purulent discharge associated with bacterial conjunctivitis and viscous and serous discharges found in viral conjunctivitis.

4.6.1 Subtype Specific Symptoms

4.6.1.1 SAC and PAC

Most people with allergic conjunctivitis have problems with both eyes. Symptoms may appear quickly, soon after the eyes have come into contact with the allergen. In other cases, as with some eye drops, symptoms may take from 2–4 days to appear. The following symptoms are most typical for allergic conjunctivitis:

- Eyes become red/pink
  By far the most common symptom. The eyes become irritated as the capillaries (small blood vessels) in the conjunctiva widen.
- Pain
  Some people have pain in one or both eyes. If the eyes are very red and painful, it is important to see a doctor. Any patient with painful, red eyes, and has become sensitive to light (photophobia), and feels his/her vision is affected should see a doctor straight away.
- Itchiness
  As the eyes are irritated they may itch, the itch may worsen if you keep rubbing them.
- Swollen eyelids
  The eyelids may puff up when the conjunctiva becomes inflamed or if the sufferer has been rubbing them a lot.
- Soreness
  The inflammation may make the whole area feel sore and tender. Some people say the soreness feels like burning.

People with seasonal allergic conjunctivitis will experience symptoms at certain times during the year, usually from early spring, into summer, and even into autumn. Those with perennial allergic conjunctivitis are susceptible at any time of year and may find certain times of the day are worse than others. If the eyelids are red, cracked, and/or dry, it is an indication that the patient most likely has contact conjunctivitis (Allansmith et al. 1977).

4.6.1.2 VKC

VKC is characterized by symptoms coined the term "morning misery" which described the active disease state of patients with severe itching, photophobia, foreign body sensation, mucous discharge (often described as "ropy"), tearing, blepharospasm, mucous discharge leaving them incapacitated upon awakening and "frequently resulting in lateness for school" and blurring of vision. It is typically bilateral but may be asymmetric in nature. While VKC is typically seasonally recurrent (hence the name vernal meaning springtime), 23% of patients may have a perennial form of them disease and many may have recurrences outside of the springtime (Kumar 2009). VKC is a severe allergic conjunctival disease with proliferative lesions in the conjunctiva. The proliferative lesion has giant papillae at the upper palpebral conjunctiva, limbal proliferation (limbal gelatinous hyperplasia and Horner-Trantas dots), and corneal lesions at high rates and easily becomes severe. Photophobia due to chronic keratitis is also common. Characteristic corneal lesions include exfoliated superficial punctate keratitis, shield ulcer (shield-shape ulcer), and corneal plaque. Clinical diagnosis is easy because the symptoms are characteristic. Major single-causative antigens are house dust mite, and the reaction with multiple kinds of antigens such as pollens and animal scurf occurs frequently.

4.6.1.3 AKC

In AKC, unlike VKC, the symptoms are perennial. There may be seasonal variation, however,

with worsening symptoms during winter months. The single most common symptom is bilateral itching of the eyelids, but watery discharge, redness, photophobia, and pain may be associated. Ocular signs of VKC commonly are seen in the cornea and conjunctiva. In contrast to AKC, the eyelid skin usually is not as significantly involved (Chen et al. 2014; Kumar 2009).

4.6.1.4 GPC

Primary symptoms in GPC are ocular itching with a mucoid or ropy discharge, very similar to that seen in VKC. Another symptom of GPC may be persistent foreign body sensations when using contact lenses, resulting in a decrease wear time and potential reduction in the visual acuity. Contact lens intolerance is especially problematic in patients with keratoconus who are highly dependent on contact lenses for optimal visual function (Allansmith et al. 1977).

4.7 Objective

Conjunctival hyperemia with dilated conjunctival vessels is the most frequent conjunctival finding. Conjunctival swelling is a finding that is induced by circulatory failure of the palpebral conjunctival vessels and lymphatic vessels. And in many cases, conjunctival opacity is accompanied. A conjunctival follicle is a lymphoid follicle seen under the lower palpebral conjunctival epithelium. This finding can be discriminated from papillae by the condition of a smooth dome-like prominence, which is surrounded by vessels. Conjunctival papillae are originated from epithelial proliferation in response to inflammation, in which the epithelium itself is hypertrophic. A vascular network is present from the center of the prominence, although this network is seen at the upper palpebral conjunctival fornix physiologically. Papillae of 1 mm or more in diameter, called giant papillae, are fibrous proliferative tissues found typically in VKC and GPC, and a large number of inflammatory cells such as lymphocytes, mast cells, and eosinophils are observed under the epithelium. Conjunctival edema is caused by leakage of plasma components from the vessels. Horner-Trantas dots found at the limbal region are small prominences induced by degeneration of proliferated conjunctival epithelium, in which congregated eosinophils may be present. Corneal complications in severe cases include superficial punctate keratitis, which is a partial defect of the corneal epithelium, exfoliated superficial punctate keratitis, and shield ulcer (shield-shape ulcer), which is a prolonged corneal epithelial defect.

4.7.1 Clinical Evaluation Criteria of Objective Findings

Major objective symptoms in each site of the palpebral conjunctiva, bulbar conjunctiva, limbal conjunctiva, and cornea were graded for severity and the clinical evaluation criteria were made.

4.7.1.1 Palpebral Conjunctiva

The items evaluated in palpebral conjunctival findings are hyperemia, swelling, follicles, papillae, and giant papillae. The criteria in each item are the density of dilated blood vessels for hyperemia, the scale and the presence or absence of opacity for swelling, the number of follicles in either side inferior palpebral conjunctiva where more follicles are observed than in the other side for follicle. Papillae are evaluated according to their diameter.

GPC is an immune-mediated inflammatory disorder of the superior tarsal conjunctiva. The initially small papillae eventually coalesce with expanding internal collections of inflammatory cells. As the name implies, the primary finding is the presence of "giant" tarsal papillae, which are typically greater than 0.3 mm in diameter. The most salient feature of GPC is the presence of giant papillae on the upper tarsal conjunctiva. Giant papillae are arbitrarily defined as papillae with a diameter greater than 1.0 mm, the condition is referred to as giant papillary conjunctivitis. Macropapillae (papillae with a diameter of 0.3–1.0 mm) are also abnormal (Ebert 1990). Also in VKC, the papillar findings are also graded as severe. In case with papillae of 1 mm or more in diameter, it is regarded as giant papillae, which are evaluated according to the prominence range (Chen et al. 2014).

4.7.1.2 Bulbar Conjunctiva

The bulbar conjunctiva is evaluated according to hyperemia and chemosis. Since pathologic conditions are characterized by marked hyperemia, the grade of "severe" hyperemia is defined as entire vascular dilation. Chemosis is evaluated according to its shape.

4.7.1.3 Limbal Conjunctiva

The Horner-Trantas dots is evaluated according to the number of the dots seen over the entire limbal region, and the swelling is evaluated according to the range of the salmon pink swelling observed at the scleral side of the limbus.

4.7.1.4 Cornea

The severity of the corneal epithelial defect is used as evaluation criteria. It is assumed in corneal disorders that superficial punctate keratitis is mildest and exfoliated superficial punctate keratitis is the next grade, and corneal erosion and shield ulcer follow in severity. Degenerated epithelium and mucin are deposited on the surface of the cornea and are observed as corneal plaque when corneal epithelium disorder persists. Because the condition may persist even after the inflammation is alleviated, the presence or absence of defective epithelium was not included in the grading evaluation.

4.8 Examinations

The objective of clinical examinations is to prove a type I allergic reaction in the conjunctiva and in the whole body. Clinical test methods for proving type I allergic reactions in the conjunctiva include the identification of eosinophils in the conjunctiva, instillation provocation test, and total IgE antibody measurements in lacrimal fluid. Systemic allergy tests detect antigen specific IgE antibodies in the skin and serum (Allansmith 1977).

Nonspecific examinations for type I allergy:

- Blood count of eosinophils
- Serum total IgE antibody (RIST: radioimmunosorbent test)
- Total IgE antibody measurement in lacrimal fluid
- Identification of eosinophils in the conjunctiva

Specific examinations for type I allergy:

- Serum specific IgE antibody (RAST: radioallergosorbent test)
- Histamine releasing test
- Basophil activation test
- Instillation provocation test
- Intracutaneous test
- Scratch test
- Prick test

4.9 Pathology: Histologic Findings

Allergic keratoconjunctivitis is a group of distinctive clinical disorders that are largely IgE-mediated hypersensitivity reactions but have quite similar histopathology.

As seen in the photograph, the epithelium is thickened and spongiotic, which intercellular edema or as seen here separation of epithelial cells. There is significant hyperemia with numerous eosinophils in chronic inflammatory infiltrate. However, most important is the exocytosis of eosinophils within the epithelium. The surface shows a desquamation of epithelium and inflammatory cells. Limbal papillae may occur in vernal keratoconjunctivitis (Horner-Trantas dots).

4.9.1 AKC

Conjunctival scrapings of patients with AKC may demonstrate the presence of eosinophils, although the number is not as significant as that seen in VKC. Additionally, free eosinophilic granules, which are seen in VKC, are not seen in AKC. Mast cells also may be found within the substantia propria of the conjunctiva in greater numbers (Singh et al. 2010). There is an increased amount of IgE in the tears of patients with AKC. Although AKC is typically recognized as a type I hypersensitivity reaction, evidence has been found that supports some involvement of type IV hypersensitivity reaction, as is the case in VKC.

4.9.2 VKC

Conjunctival scrapings of the superior tarsal conjunctiva show an abundance of eosinophils. Conjunctival biopsy reveals that there are a large number of mast cells within the substantia propria. Histochemical analysis of mast cells, present in VKC, reveals neutral proteases tryptase and chymase. There is an enhanced fibroblast proliferation, which leads to the deposition of collagen within the substantia propria and, as a result, induces conjunctival thickening. B-cell and T-cell lymphocytes are present locally, which combine to produce IgE. Increased total IgE antibodies in serum and lacrimal fluid and positive results for serum antigen specific IgE antibody are detected at high rates. In addition, a high positive rate of eosinophils in the conjunctival smear is found. Consequently, the definitive diagnosis is easy. Specific IgE and IgG as well as the inflammatory mediators histamine and tryptase have been isolated from tears of patients with VKC. Although VKC is typically recognized as a type I hypersensitivity reaction, evidence has been found that supports some involvement of type IV hypersensitivity reaction (Singh et al. 2010).

4.9.3 GPC

Immediate hypersensitivity of IgE-dependent anaphylactic mechanisms alone cannot account for the histologic picture in GPC. Histologic findings in GPC consist of cellular infiltration of the conjunctiva by a number of cell types. Plasma cells, lymphocytes, mast cells, eosinophils, and basophils have been identified within the substantia propria. Mast cells also may be found in the epithelium. There is also elevated tear levels of immunoglobulin, especially IgE and tryptase also are elevated, as in AKC and VKC. The degree of mast cell degranulation and tissue edema and the increase in eosinophils seen in IgE anaphylactic reactions do not include such features of GPC as increased tissue mass, presence of many inflammatory cells, extensive infiltration with eosinophils, increased number of mast cells in the substantia propria and epithelium, and the presence of basophils. The cellular infiltrate of giant papillary conjunctivitis and vernal conjunctivitis suggests a common immunologic basis for the two diseases. The mechanism of GPC is probably a basophil-rich delayed hypersensitivity (similar to cutaneous basophilic hypersensitivity) with a possible IgE humoral component. In (genetically) predisposed individuals, irritation caused by the foreign body combined with grinding the antigen repeatedly against the conjunctiva is thought to trigger a hypersensitivity response (Ebert 1990). Mechanical trauma is important in the pathogenesis of GPC. The condition is nearly universally present in patients with ocular prosthesis in whom excess mucous production can be observed. Abrasion of the upper palpebral conjunctiva by exposed suture ends (suture barb giant papillary conjunctivitis) has been reported and resolves with removal or trimming of the offending sutures). Studies of the ultrastructure of tissues from GPC patients and vernal conjunctivitis patients disclosed that patients with vernal conjunctivitis have more mast cells in the epithelium and substantia propria of the conjunctiva than do patients with GPC and that the mast cells are more completely degranulated (Allansmith et al. 1977). The greater number of mast cells in vernal conjunctivitis can explain the further findings of greater mediator-associated changes: higher tear histamine levels, more eosinophils, greater itching and inflammation, and more corneal pathology.

4.10 Diagnosis

Diagnosis of allergic conjunctivitis generally is made by taking a thorough history and by careful clinical observation. In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective symptoms and objective findings accompanying allergic inflammation. The diagnosis is ensured by proving a type I allergic reaction in the conjunctiva. Frequent subjective symptoms are ocular itching, hyperemia, eye discharge, foreign body sensation, ocular pain, and photophobia. The ocular itching is the most common among all

inflammatory symptoms accompanying type I allergic reactions and is important as a basis for diagnosis. Other important symptoms are hyperemia, eye discharge, and lacrimation, although those symptoms are not specific for allergic conjunctival diseases. Foreign body sensations, ocular pain, and photophobia are symptoms accompanying corneal lesions and indicate the severity of the inflammation rather than its diagnostic significance. Giant papillae, limbal proliferation (limbal gelatinous hyperplasia, Horner-Trantas dot), and shield ulcer are important objective symptoms. Conjunctival edema and follicles, papillary hyperplasia, and corneal epithelial abrasion (corneal erosion and exfoliated superficial punctate keratitis) are "intermediately specific," and conjunctival hyperemia and superficial punctate keratitis are "poorly specific." However, the symptoms and findings that form the basis of diagnoses are slightly different among the diseases as shown in Fig. 5.

4.10.1 SAC

A clinical diagnosis can be made by subjective symptoms including ocular itching, lacrimation, hyperemia, and foreign body sensation and objective symptoms including conjunctival hyperemia, conjunctival edema, and conjunctival follicles, which are found annually during the same season. The most common and important symptom of SAC is the ocular itching. Since the majority of SAC cases are conjunctivitis caused by pollen antigens, complicated symptoms of rhinitis are observed in 65–70% of cases. A positive test for serum antigen specific IgE antibody or a positive skin reaction, even in quasi-definitive diagnoses, makes it highly probable that a definite clinical diagnosis can be made. The serum total IgE antibody may be normal or mildly increased. The positive agreement rate in the measurement of the total IgE antibody in lacrimal fluid is about 70%. The exposure to a large amount of antigens may induce acute bulbar conjunctival edema. Classic signs of allergic conjunctivitis include injection of the conjunctival vessels as well as varying degrees of chemosis (conjunctival edema) and eyelid edema. The conjunctiva often has a milky appearance due to obscuration of superficial blood vessels by edema within the substantia propria of the conjunctiva. Edema is generally believed to be the direct result of increased vascular permeability caused by release of histamine from conjunctival mast cells.

4.10.2 PAC

A multiseasonal or almost perennial ocular itching, lacrimation, hyperemia, and eye discharge are subjective symptoms of PAC and conjunctival hyperemia and papilla without proliferative change in the conjunctiva are objective symptoms. Most cases pass over chronically. The major antigens are house dust mite. Because it is very likely that the clinical symptoms are mild and characteristic objective symptoms are lacking, clinical diagnosis can be difficult in some cases, especially in elderly cases. Since the positive rate of eosinophils in the conjunctival smear is low, repetitive testing becomes necessary for the proof in some cases.

4.10.3 AKC

In AKC, the atopic dermatitis is complicated with facial lesions and conjunctivitis is perennially chronic with ocular itching, eye discharge, papillary hyperplasia, and corneal lesions. Proliferative lesions such as giant papillae and limbal lesions are present in some cases. Long-term chronic inflammation may result in fornix foreshortening and symblepharon. AKC may affect eyelid skin and lid margin, conjunctiva, cornea, and lens. Skin of the eyelids may exhibit eczematoid dermatitis with dry, scaly, and inflamed skin and the lid margins may show meibomian gland dysfunction and keratinization. Moreover, staphylococcal colonization of eyelid margins is very common in AKC and may result in blepharitis. Conjunctiva may show chemosis and typically a papillary reaction, which is more prominent in the inferior tarsal conjunctiva, in contrast to that seen in vernal keratoconjunctivitis. Fibrosis or scarring of the

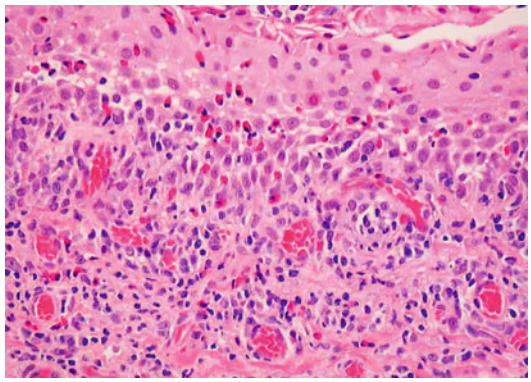

Fig. 4 Allergic keratoconjunctivitis and blepharitis inflamed by upper eyelid skin. Hematoxylin and eosin (H-E) staining. There is significant hyperemia with significant eosinophils in chronic inflammatory infiltrate. The epithelium of palpebral conjunctiva is thickened and spongiotic, which intercellular edema or as seen here separation of epithelial cells

conjunctiva may result in a shortened fornix or symblepharon formation with chronic inflammation. Corneal involvement ranges from PEK, early in the course of the disease, to neovascularization, stromal scarring, and possibly ulceration. There is also a strong association between AKC and herpes simplex labialis and herpes simplex viral keratitis. Increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody are found at high rates. As seen in VKC patients, the chronic eye rubbing of the cornea may contribute to the development of keratoconus. Characteristic lenticular changes in AKC include anterior or posterior subcapsular cataract formation. These slow progressing lens opacities are usually bilateral and present in the second decade of life. There is some reasonable speculation that the long-term use of topical corticosteroids can also induce the lenticular changes later in life (Fig. 4).

4.10.4 VKC

The classic conjunctival sign in palpebral VKC is the presence of giant papillae. VKC may be subdivided into two varieties as follows: palpebral and limbal. The papillae most commonly occur on the superior tarsal conjunctiva; usually, the inferior tarsal conjunctiva is unaffected. Giant papillae assume a flattop appearance, which often is described as "cobblestone papillae." In severe cases, large papillae may cause mechanical ptosis (drooping eyelid). The astute clinician's attention is always drawn to the everted upper tarsus, which reveals key telltale signs, including papillae, vascular abnormalities, conjunctival inclusion cysts, follicles, subconjunctival scarring, and entropion. A ropy mucous discharge may be present, which commonly is associated with tarsal papillae. Large numbers of eosinophils, indicating the presence of extended periods of inflammation, are present in the discharge. As the name implies, papillae tend to occur at the limbus, the junction between the cornea and the conjunctiva, and have a thick gelatinous appearance. They commonly are associated with multiple white spots (Horner-Trantas dots), which are collections of degenerated epithelial cells and eosinophils. Horner-Trantas dots rarely last longer than a week from their initial presentation and generally resolve rapidly with the initiation of topical corticosteroid therapy. While corneal vascularization is rare, the cornea may be affected in a variety of ways. Punctate epithelial keratopathy (PEK) may result from the toxic effect of inflammatory mediators released from the conjunctiva. The appearance of PEK may be a precursor for the characteristic shield ulcer, which is pathognomonic of VKC. PEK can coalesce, resulting in frank epithelial erosion and forming into a shield ulcer, which is typically shallow with white irregular epithelial borders. Although the pathogenesis of a shield ulcer is not well understood, the major factor in promoting development may be chronic mechanical irritation from the giant tarsal papillae. Some evidence suggests that the major basic protein released from eosinophils may also promote ulceration. Another type of corneal involvement is vernal pseudogerontoxon, which is a degenerative lesion in the peripheral cornea resembling corneal arcus. Keratoconus may be seen in chronic cases, which may be associated with chronic eye rubbing in predisposed individuals.

4.10.5 GPC

In cases of contact lenses, ocular prosthesis, or surgical sutures, clinical diagnosis of GPC is made when ocular itching, foreign body sensations, and eye discharge are present and conjunctival hyperemia, conjunctival edema, and papillary hyperplasia are found. GPC induced by contact lenses is called contact lens related papillary conjunctivitis. Early diagnosis is an essential component of the treatment of GPC. But, unfortunately, the earliest clues to the development of GPC in soft lens wearers are minor and are usually dismissed by patients as inconsequential: increased mucus in the nasal corner of the eye on arising and itching immediately after removing the lens. Patients, thinking that these minor signs and symptoms are "normal," may never report them to their physicians. In more severe stages of GPC, patients may complain of mild blurring of vision after hours of wearing the lens (from deposits on the lens and not corneal edema), readily apparent excess mucus, and movement of the lens on blinking. In advanced stages of GPC, patients cannot tolerate the foreign body sensation of pain associated with wearing the contact lens. Sheets or strings of mucus are present, sufficient sometimes to glue the eyes shut on waking in the morning. At this stage, the lenses are visibly clouded by mucus soon after they are inserted. Abnormal amounts of deposits on the soft lenses are a constant feature of the syndrome. Deposits on the lens are most easily seen by drying the lens slightly and looking through it against a light. Although some asymptomatic wearers of soft contact lenses may also produce heavy deposits on their soft lenses, all symptomatic wearers do. Usually, patients report the symptoms of GPC long before the appearance of definitive clinical signs. Furthermore, patients vary widely in how much ocular discomfort they will tolerate from various degrees of GPC. Some patients may continue wearing their soft contact lenses despite scores of giant papillae covering both upper tarsal plates. Other patients may stop wearing their soft contact lenses because of the itching and increased mucus, although the only definitive sign of GPC is conjunctival thickening. Such patients will complain of lens intolerance even though no giant papillae are apparent. Early in the clinical stage of GPC, the normally small papillae become obscured by more elevated ones. Small normal papillae do not enlarge to become giant papillae; new abnormal papillae begin to grow from the substructure of the deep conjunctival or tarsal area. At this point, there is a generalized thickening of the conjunctiva. The conjunctiva has a translucent rather than transparent appearance, and the vasculature of the plate becomes more visible. The conjunctiva may appear hyperemic. Giant papillary conjunctivitis represents the most severe cases, which present with giant papillae of 1 mm or larger in diameter. The involvement of type I allergy is unknown in some cases and positive results for serum antigen specific IgE antibody are not frequent. A positive rate of eosinophils in GPC is rarer than that in other allergic conjunctival diseases. Examination of superior tarsal conjunctiva reveals the presence of large cobblestone papillae, which are generally 0.3 mm or greater in diameter. In the more aggravated stage of GPC, the conjunctiva loses translucency to become more opaque (due to cellular infiltration), and it is possible to observe the earliest demarcations of macropapillae (0.3–1.0 mm) or giant papillae (1.0 mm or greater) (Ebert 1990). As the disorder progresses, giant papillae increase in size and elevation. The surface flattens to produce a mushroom appearance devoid of remnants of the small papillary pattern. As the number and size of giant papillae increase, they may almost completely cover zones 1 and 2 with papillae ranging in size from 0.6 to 1.75 mm in diameter, with most approximately 0.75–1.0 mm in diameter. Papillae and follicles resemble each other in some respects, and both are signs of active inflammation in the palperbral conjunctiva. Giant papillae are distinguished from follicles, however, by the presence of blood vessels in the centers of the follicles as well as around the edges. Follicles are more commonly observed in the inferior palpebral conjunctiva and the inferior fornix. Papillae are more commonly observed in the upper palpebral conjunctiva. The side walls of papillae are often perpendicular to the plane of the tarsal plate and not pyramidal-like follicles. Papillae may have

white heads resembling scars. These white, scar-like areas usually regress as the papillae regress. Some patients with GPC may have Horner-Trantas dots. A network of fine dilated blood vessels may be observed in GPC. The disease may also be confined to the limbus in some patients, with no infiltration of the lid.

4.11 Differential Diagnosis

Ocular itching is a cardinal symptom of allergic eye disease and in the absence of itching, an alternative diagnosis should be suspected. Allergic conjunctivitis must be differentiated from viral and bacterial conjunctivitis. Clinical features (e.g., recent exposure to an individual with infective conjunctivitis) may be helpful in this regard (Fig. 5). Infectious conjunctivitis such as viral, bacterial, Chlamydia, non-inflammatory conjunctival folliculosis, and dry eye are considered as differential diagnosis. Also, differential diagnosis is also necessary for ocular and conjunctival symptoms associated with contact dermatitis (Friedlaender 1998; Niederkorn 2008). The main distinction between seasonal and perennial allergic conjunctivitis, as implied by the names, is the timing of symptoms. Major differentiating factors between AKC and VKC, and other diseases are as references are shown in Table 2.

4.12 Treatments

Avoidance of the offending antigen is the primary behavioral modification for all types of allergic conjunctivitis. Perennial avoidance and elimination of antigens can be achieved by arranging the patient's daily living environment, especially their indoor environment. In contrast, the avoidance of pollen antigens is conducted mainly during the pollen-flying period, and it is necessary to take measures so that the daily activities of the patient will not be prevented by exposure to pollens. During pollen-flying period, goggle-type glasses are recommended to carry out daily activities such as riding a bicycle and having a stroll with a dog, although even glasses themselves can reduce

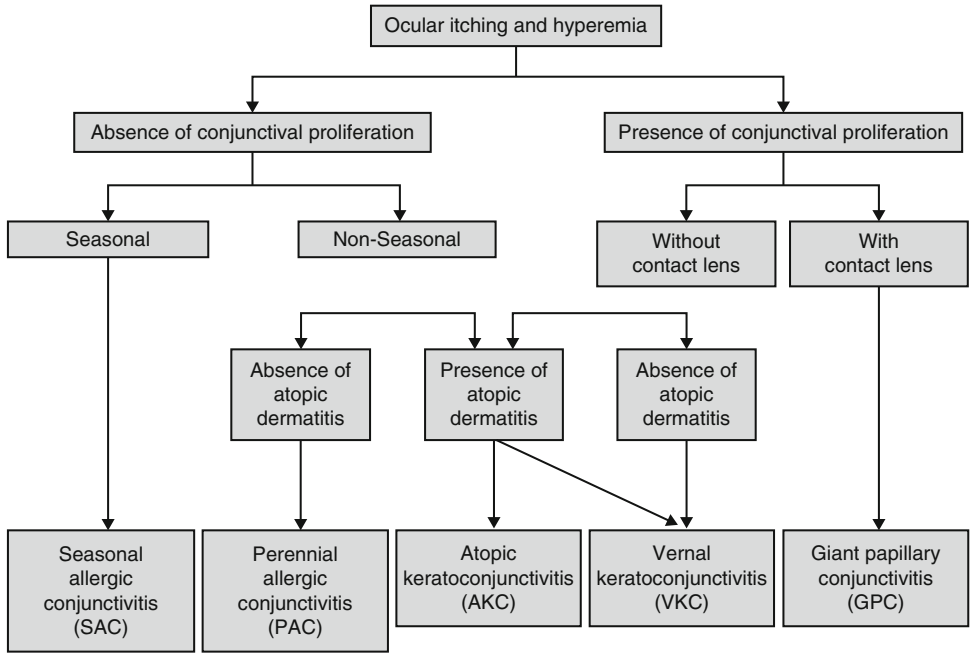

Fig. 5 Diagnostic flowchart of allergic conjunctival diseases. (Japanese Society of Allergology) http://www.allergologyinternational.com/article/S1323-8930(16)30173-3/fulltext#cebib0010

the amount of pollen flying into the ocular surface. In other respects, management of allergic conjunctivitis varies somewhat according to the specific subtypes. During the pollen-flying period, it is useful to stop inserting contact lenses as much as possible, changing to glasses to avoid antigens (Table 3).

In seasonal and perennial allergic conjunctivitis, superficial conjunctival scrapings may help to establish the diagnosis by revealing eosinophils, but only in the most severe cases, since eosinophils are typically present in the deeper layers of the substantia propria of the conjunctiva. Therefore, the absence of eosinophils on conjunctival scraping does not rule out the diagnosis of allergic conjunctivitis. Many investigators have described measurement of tear levels of various inflammatory mediators, such as IgE, histamine, and tryptase, as indicators of allergic activity (Bielory et al. 2012). Additionally, skin testing by an allergist may provide definitive diagnosis and pinpoint the offending allergen(s). Skin testing is now highly practical and readily available to all practicing ophthalmologists, as well as to optometrists in some states. Allergy-specific tear and conjunctival scraping laboratory tests are not currently available except in academic or commercial research settings. Similarly, impression cytology techniques are potentially enlightening yet available to only a few dedicated research centers and ophthalmology-specific diagnostic laboratories. Conjunctival scrapings can be sent to hospital cytology laboratories and may be useful if a pathologist with a particular interest in ocular diseases is readily available.

Drug treatment is the preferred treatment for allergic conjunctival diseases. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. Pharmacologic intervention may be necessary to help alleviate the symptoms of acute allergic conjunctivitis. Various classes of medication may be effective against the symptoms of acute allergic conjunctivitis; each is directed at a specific point in the inflammatory and allergic cascade. Allergic conjunctivitis can be treated with a variety of drugs. These include

Table 3 Risk factors

Grouping	Type	Risk factors
Without corneal involvement	Acute	Environmental allergens, particularly if they are known; an example is cat dander
	Seasonal	Environmental allergens that are often associated with changes in seasons; examples include grass and weed pollens
	Perennial	Environmental allergens that occur throughout the year; examples include indoor allergens: dust mites, mold, animal dander
With corneal involvement	Vernal	Environmental allergens may incite an acute exacerbation. Most commonly present during the springtime with the associated increase in pollen. Increased presence in hot and dry environments with a decrease in inflammation and symptoms during the winter months
	Atopic	Genetic predisposition to atopic reactions with comorbid asthma and atopic dermatitis commonly present. Increased risk with positive family history. Environmental allergens may cause an acute exacerbation as well. No changes with seasons
	Giant papillary	Commonly seen in individuals wearing soft contact lens who infrequently replace their lenses, wear their lenses for prolonged periods of time, have poor lens hygiene, have poor contact lens fitting, or are allergic to the various contact lens solution. Similarly, irritation from exposed sutures or prostheses increases the risk for developing GPC

Citation: http://eyewiki.aao.org/Allergic_conjunctivitis. American Academy of Ophthalmology Eye Wiki, 2014

topical antihistamines, mast cell stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. As always, care must be taken when using topical corticosteroids; pulsed regimen is recommended to minimize adverse reactions.

In VKC, conjunctival scrapings of the superior tarsal conjunctiva and of Horner-Trantas dots show an abundance of eosinophils. Conjunctival scrapings of patients with AKC may demonstrate the presence of eosinophils, although the number is not as significant as that seen in VKC. Additionally, free eosinophilic granules, which are seen in VKC, are not seen in AKC. For severe AKC and VKC, additional use of immunosuppressive eye drops, steroid oral medicines, subtarsal conjunctival steroid injection and surgical treatment such as papillary resection should be considered. Advanced point-of-service testing may soon become available through several diagnostic technology companies. Biomarkers such IgE, matrix metalloprotease-9 (MMP-9), or eosinophilic basic protein (EBP) may prove to be clinically useful surrogates for disease activity level and therapeutic response monitoring. Specimens can be obtained by tear sampling or conjunctival scraping techniques (Table 4).

4.12.1 Subtarsal Conjunctival Injection of Steroid Suspension

Triamcinolone acetonide or betamethasone suspension is injected to the subtarsal conjunctiva of the upper eyelid in intractable or severe cases. With caution for the elevation of intraocular pressure, it is desirable to avoid repeated use or the application to children aged less than 10 years.

4.12.2 Ophthalmic Lubricants

Lubricants act as humectants in the eye. Artificial tear, as mentioned below, substitutes provide a barrier function and help to improve the first-line defense at the level of conjunctival mucosa. The ideal artificial lubricant should be preservative-free; contain potassium, bicarbonate, and other electrolytes; and have a polymeric system to increase its retention time. Lubricating drops are used to reduce morbidity and to prevent complications. Lubricating ointments prevent complications from dry eyes. Ocular inserts reduce symptoms resulting from moderate to severe dry eye syndromes.

4.12.3 Artificial Tears: Altalube, Bion Tears, HypoTears, LiquiTears, Soothe, Systane, Tears Again, Viva-Drops

Artificial tears are used to increase lubrication of the eye. Nonpreserved artificial tears are recommended for use. Tears should be applied liberally throughout the day, and, if necessary, a lubricating ointment may be used at night. These agents help to dilute various allergens and inflammatory mediators that may be present on the ocular surface, and they help flush the ocular surface of these agents. Chilled tears, as well as any topical medication, provide an added degree of relief. Similarly, cold compresses can be extremely useful to avoid the customary irrational rubbing response to chronic or paroxysmal pruritus.

4.12.4 Antiallergic Eye Drops

Histamine H1 receptor antagonists block histamine H1 receptors, representative mediators released through the degranulation of mast cells, which results in suppression of hyperemia and ocular itching. Mast cell stabilizer inhibits the degranulation of mast cells and suppresses release of mediators (e.g., histamine, leukotriene, thromboxane A2), consequently, the early phase reaction to type I allergy is inhibited, and conjunctival local infiltration of inflammatory cells is curtailed, resulting in a reduction of the late phase reaction.

4.12.5 Antihistamines

These agents act by competitive inhibition of histamine at the H1 receptor and thus block the

Table 4 Differential diagnosis

Infectious conjunctivitis
A variety of microorganisms, such as viral, bacterial, and *Clamydia*, may infect the conjunctiva. Viral and bacterial conjunctivitis are quite contagious, easily passing from one person to another, or from a person's infected eye to the uninfected eye
Phlyctenular keratoconjunctivitis
Phlyctenular keratoconjunctivitis has been defined as a nodular inflammation of the cornea or conjunctiva that results from a hypersensitivity reaction to a foreign antigen, which is postulated to occur secondary to an allergic, hypersensitivity reaction at the cornea or conjunctiva, following reexposure to an infectious antigen that the host has been previously sensitized to
Toxic conjunctivitis
Typically, toxic conjunctivitis occurring with protracted use of topical ocular medications. Toxic ocular reactions are most frequently reported in patients with glaucoma, especially who are on lifelong therapy with multiple medications
Contact dermatitis
Contact dermatitis is not an IgE-mediated allergy and can be considered in a different category than the before mentioned allergic conditions (Molinari 1982). Allergens are generally simple chemicals, low molecular weight substances that combine with skin protein to form complete allergens. Examples include poison ivy, poison oak, neomycin, nickel, latex, atropine and its derivatives. Contact allergy involves the ocular surface, eyelids and periocular skin, although contact allergic reactions usually occur on the skin, including the skin of the eyelids, the conjunctiva may also support contact allergic reactions. Initial sensitization with a contact allergen may take several days. Upon reexposure to the allergen, an indurated, erythematous reaction slowly develops. The reaction may peak 2–5 days after reexposure. The delay in development of the reaction is due to the slow migration of lymphocytes to the antigen depot. The term "delayed hypersensitivity" is sometimes given to these reactions, in contrast to "immediate hypersensitivity," a term which emphasizes the rapid development of IgE antibody-mediated reactions. Contact allergic reactions are generally associated with itching. Treatment consists of withdrawing and avoiding contact with allergen. Severe reactions can be treated with topical or systemic corticosteroids. It is a type-IV delayed hypersensitivity response, that occurs through interaction of antigens with Th1 and Th2 cell subsets followed by release of cytokines (Kashima et al. 2014). It consists of two phases: sensitization at the first exposition to the allergen, with production of memory T-lymphocytes), and elicitation of the inflammatory response at the reexposure to the antigen, mediated by the activation of memory allergen-specific T-lymphocytes
Non-inflammatory conjunctival folliculosis
Conjunctival folliculosis is a fairly common benign, bilateral, non-inflammatory disorder characterized by follicular hypertrophy of the palpebral conjunctivae. Vessels are present at the edge of the follicle, in contrast to conjunctival papillae
Keratitis
Keratitis is an inflammation of the cornea sometimes caused by an infection involving bacteria, viruses, fungi, or parasites. Noninfectious keratitis can be caused by a minor injury, wearing your contact lenses too long, or other noninfectious diseases
Blepharitis
One of the most common ocular conditions characterized by inflammation, scaling, reddening, and crusting of the eyelid
Dry eyes syndrome
Dry eye syndrome is caused by a chronic lack of sufficient lubrication and moisture on the surface of the eye. Consequences of dry eyes range from subtle but constant eye irritation to significant inflammation and even scarring of the front surface of the eye
Ocular rosacea
Chronic inflammatory acneiform skin condition that leads to erythema of the skin on the face and neck. It is thought to represent a type IV hypersensitivity reaction **(**Table 1**)**
Episcleritis/scleritis
Episcleritis and scleritis are inflammatory conditions which affect the eye. Scleritis is much more serious and less common than episcleritis. Episcleritis affects only the episclera, which is the layer of the eye's surface lying directly between the clear membrane on the outside (the conjunctiva) and the firm white part beneath (the sclera). Scleritis affects the sclera and, sometimes, the deeper tissues of the eye. Both can be associated with other conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE), although this is more likely in the case of scleritis. Episcleritis does not cause scleritis, although scleritis can lead to associated episcleritis

(*continued*)

Table 4 (continued)

Angle closure glaucoma
Glaucoma is a nonspecific term used for several ocular diseases that ultimately result in increased intraocular pressure and decreased visual acuity. Primary angle closure is defined as an occludable drainage angle and features indicating that trabecular obstruction, which results in increased intraocular pressure, by the peripheral iris has occurred. The term glaucoma is added if glaucomatous optic neuropathy is present. The sudden and severe intraocular pressure elevation can quickly damage the optic nerve, resulting in acute angle-closure glaucoma

effects of endogenously released histamine. Systemic and/or topical antihistamines may be prescribed to relieve acute symptoms due to interaction of histamine at ocular H1 and H2 receptors (Gonzalez-Estrada et al. 2017). While systemic antihistamines often relieve ocular allergic symptoms, patients may experience systemic adverse effects, such as drowsiness and dry mouth.

- Emedastine difumarate (Emadine®)
  This agent is a relatively selective H1 receptor antagonist for topical administration. The 0.05% ophthalmic solution contains 0.884 mg/mL of emedastine difumarate.
- Epinastine (Elestat®)
  A direct H1 receptor antagonist, epinastine does not penetrate the blood–brain barrier and therefore should not induce adverse CNS effects. It is indicated for symptoms due to allergic conjunctivitis.
- Azelastine ophthalmic
  Azelastine, now available as a generic, competes with H1-receptor sites on effector cells and inhibits release of histamine and other mediators involved in the allergic response.
- Bepotastine besilate ophthalmic solution (Bepreve®)
  Bepotastine besilate is a topically active antihistamine that directly antagonizes H1-receptors and inhibits release of histamine from mast cells. It is indicated for itching associated with allergic conjunctivitis.
- Alcaftadine ophthalmic (Lastacaft®)
  An H1-receptor antagonist indicated for prevention of itching associated with allergic conjunctivitis, alcaftadine inhibits histamine release from mast cells, decreases chemotaxis, and inhibits eosinophil activation. It is available as a 0.25% ophthalmic solution.
- Cetirizine ophthalmic (Zerviate®)
  H1 receptor antagonist inhibits histamine release from mast cells, decreases chemotaxis, and inhibits eosinophil activation. Indicated for ocular itching associated with allergic conjunctivitis. It is administered twice daily.

Topical antihistamines competitively and reversibly block histamine receptors and relieve itching and redness but only for a short time. These medications do not affect other proinflammatory mediators, such as prostaglandins and leukotrienes, which remain uninhibited. A number of topical antihistamines are available, including epinastine (Elestat) and azelastine (Optivar®). Both are potent antihistamines that have a rapid onset and are effective in relieving the signs and symptoms of allergic conjunctivitis.

4.12.6 Mast Cell Stabilizers

Mast cell stabilizers inhibit the degeneration of sensitized mast cells when exposed to specific antigens by inhibiting the release of mediators from the mast cells (Finn and Walsh et al. 2013). The end result is a decrease in degranulation of mast cells, which prevents release of histamine and other chemotactic factors that are present in the preformed and newly formed state. Note that mast cell stabilizers generally do not relieve existing symptoms and are to be used on a prophylactic basis to prevent mast cell degranulation with subsequent exposure to the allergen. Therefore, they need to be used long term in conjunction with various other classes of medications. Common mast cell stabilizers include cromolyn sodium and lodoxamide (Alomide). Alcaftadine (Lastacaft), bepotastine (Bepreve®), olopatadine

(Patanol®), nedocromil (Alocril®), and ketotifen (Zaditor®) are also mast cell stabilizers with additional antihistamine properties and proactively inhibit histamine release while blocking subsequent distal pathway histamine receptors. These agents block calcium ions from entering the mast cell. Olopatadine is a relatively selective H1 receptor antagonist and inhibitor of histamine release from mast cells.

- Lodoxamide tromethamine (Alomide®)
  Lodoxamide is a mast cell stabilizer. The active ingredient in this product is 1.78 mg lodoxamide tromethamine.
- Olopatadine (Patanol®, Pataday®, Pazeo®)
  Olopatadine is a relatively selective H1 receptor antagonist and inhibitor of histamine release from mast cells. The active ingredient of Patanol is 1.11 mg olopatadine hydrochloride; Pataday is 2.22 mg olopatadine hydrochloride.
- Ketotifen (Zaditor®, Alaway®)
  Ketotifen is an over-the-counter (OTC) antihistamine eye drop. It is a noncompetitive H1-receptor antagonist and mast cell stabilizer. This agent inhibits release of mediators from cells involved in hypersensitivity reactions.
- Nedocromil ophthalmic (Alocril®)
  Nedocromil interferes with mast cell degranulation, specifically with release of leukotrienes and platelet activating factor.

4.12.7 Vasoconstrictors

Vasoconstrictors are available either alone or in conjunction with antihistamines to provide short-term relief of vascular injection and redness. Common vasoconstrictors include naphazoline, phenylephrine, oxymetazoline, and tetrahydrozoline. Generally, the common problem with vasoconstrictors is that they may cause dependency with resultant rebound conjunctival injection and inflammation. These pharmacologic agents are ineffective against severe ocular allergies and against other more severe forms of allergic conjunctivitis, such as atopic and vernal disease. They induce chemical tolerance and progressive tachyphylaxis, thereby adding continuously increasing medication and preservative toxicity to the clinical picture.

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
  The mechanism of action of NSAIDs is believed to be through inhibition of the cyclooxygenase enzyme that is essential in the biosynthesis of prostaglandins, which results in vasoconstriction, decrease in vascular permeability and leukocytosis, and a decrease on intraocular pressure. NSAIDs act on the cyclooxygenase metabolic pathway and inhibit production of prostaglandins and thromboxanes. They have no role in blocking mediators formed by the lipoxygenase pathway, such as leukotrienes. Common NSAIDs that are approved for allergic indications include ketorolac tromethamine (Acular®).
- Ketorolac tromethamine (Acular®, Acuvail®)
  A member of the pyrrolo-pyrrole group of NSAIDs, ketorolac inhibits prostaglandin synthesis by decreasing activity of the enzyme cyclooxygenase, which results in decreased formation of prostaglandin precursors; in turn, this results in reduced inflammation. The active ingredient is 0.5% ketorolac tromethamine.

4.12.8 Corticosteroids

Corticosteroids have both anti-inflammatory (glucocorticoid) and salt retaining (mineralocorticoid) properties. Glucocorticoids have profound and varied metabolic effects (Abelson et al. 2015). In addition, these agents modify the body's immune response to diverse stimuli. Corticosteroids remain among the most potent pharmacologic agents used in the treatment of chronic ocular allergy. They act at the first step of the arachidonic acid pathway by inhibiting phospholipase, which is responsible for converting membrane phospholipid into arachidonic acid. By preventing the formation of arachidonic acid, corticosteroids effectively block both cyclooxygenase and lipoxygenase pathways, in contrast to NSAIDs, which act only on the cyclooxygenase pathway. Corticosteroids do have limitations, including

ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataract. In addition, the anti-inflammatory and immunosuppressive affects are nonspecific. As a rule, topical steroids should be prescribed only for a short period of time and for severe cases that do not respond to conventional therapy. Severe forms of ocular allergy may require chronic steroid maintenance therapy to avoid permanent structural damage to the ocular surface and central corneal stroma. Corticosteroids exist in various forms and potencies. Relatively weak steroids, such as rimexolone, medrysone, and fluorometholone, tend to have less potency in the eye, with fewer ocular adverse effects. In contrast, agents such as prednisolone acetate and difluprednate are more potent and have a higher incidence of adverse effects.

Loteprednol etabonate (Lotemax® 0.05% and Alrex® 0.02%), is an ester steroid, which is rapidly metabolized once it enters the anterior chamber of the eye. Therefore, it is extremely useful in treating ocular surface and superficial corneal inflammations owing to its favorable safety profile and therapeutic index. Alrex has a specific indication for ocular allergy and has been shown in clinical studies to have fewer ocular adverse effects. Lotemax® is indicated and FDA approved for SAC and for GPC with concomitant contact lens use.

- Loteprednol etabonate (Lotemax®, Alrex®)
  This agent decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability. It is a topical ester steroid eye drop that poses a decreased risk of glaucoma. It is available in 0.2% and 0.5% concentrations, as well as a gel formulation, a preservative-free ointment preparation, and in combination with tobramycin (Zylet®, Bausch & Lomb).

4.12.9 Immunotherapy

Immunotherapy is a mainstay in the systemic management of allergies. Traditionally, immunotherapy is delivered via subcutaneous injection (Wahn et al. 2012). However, sublingual (oral) immunotherapy (SLIT) is gaining momentum among allergists. Numerous articles have analyzed the effects of SLIT on allergic conjunctivitis. Preliminary indications are that SLIT may have a moderate effect on the signs and symptoms of allergic conjunctivitis, but further analysis is necessary. A 2012 study confirmed that SLIT may significantly reduce symptoms in children with grass pollen–allergic rhinoconjunctivitis. The preparation studied had significant effects on allergen-specific antibodies and was well tolerated.

4.12.10 Immunosuppressive Eye Drops

At present, two kinds of immunosuppressive eye drops (cyclosporine and tacrolimus) have been approved as treatment drugs for VKC. Immunosuppressive eye drops are expected to have equivalent or better effects than steroid eye drops. Cyclosporine enables the gradual reduction of the doses of steroid eye drops by combined administration with antiallergic eye drops and steroid eye drops. Tacrolimus itself also has effects on steroid-resistant severe cases (Ohashi et al. 2010).

4.13 Surgical Treatments

Severe cases of corneal shield ulcer may require superficial keratectomy to promote epithelial regeneration. This debridement also serves to obtain a direct culture specimen in the event that secondary infection ensues and helps guide prophylactic topical antimicrobial therapy. Generally, shield ulcers are chronic conditions that are often refractory to conventional therapy. There have been reports of excimer laser phototherapeutic keratectomy (PTK) being used to remove fibrin deposits on the Bowman layer and theoretically facilitate epithelial healing. Other surgical procedures, such as cryoablation of giant papillae or surgical removal of papillae with mucosal grafting, generally are not required, but they may

Table 5 Surgical therapies

Superficial keratectomy
Shield ulcer plaques, consisting of epithelial and inflammatory debris at the base of an ulcer, often are resistant to treatment with topical anti-inflammatory therapy. Superficial keratectomy may be required to remove plaques or debride shield ulcers and allow epithelialization. Medical treatment must be maintained until the cornea has reepithelialized in order to prevent recurrences
Excimer laser PTK
Excimer laser phototherapeutic keratectomy is an alternative to remove plaques or debride shield ulcers and allow epithelialization
Penetrating keratoplasty (full-thickness corneal transplant)
Corneal scarring and occasionally perforation may occur in severe cases and necessitate penetrating keratoplasty
Papillary resection
Papillary resection with or without mitomycin-C (MMC) application has been described as a method to reduce ocular surface inflammation
Surface maintenance/restoration procedures
Surface maintenance/restoration procedures may be required for severe persistent epithelial defects or ulceration. Various procedures may be
1. Amniotic membrane overlay grafting
2. Lamellar keratoplasty (partial-thickness corneal transplant)
3. Eyelid procedures such as botulinum toxin-induced ptosis or lateral tarsorrhaphy (surgical fusion of upper and lower eyelid margin to narrow the eyelid opening)
4. Gluing may be appropriate for focal ("punched-out") corneal perforations
Eyelid surgery
In advanced AKC, extensive scarring of the ocular surface and eyelid margins may necessitate eyelid surgery. This includes lid margin tightening and rotational procedures for lid mal-position, as well assymblepharon lysis and forniceal reconstruction for severe conjunctival scarring
Cataract surgery
Many patients will require cataract surgery at a relatively young age due to atopic and steroid-induced cataract development
Glaucoma surgery
A few patients may need glaucoma filtering surgery or valve placement if steroid-induced glaucoma develops
Stem cell transplantation
Patients who develop limbal stem cell deficiency may require ocular surface stem cell transplantation for visual rehabilitation. Associated systemic conditions should be treated as well. Uncontrolled dermatitis with vision-threatening complications requires systemic steroids. Any associated Herpes simplex keratitis should be treated with topical antiviral agents. Recurrent attacks of Herpes infection may require systemic antiviral also

be helpful in extremely advanced cases. Remember that since VKC is a self-limited disease, extensive reconstructive surgery may not have an acceptable risk-benefit ratio. Important surgical therapies are summarized in Table 5.

4.14 Complications

If you have seasonal or perennial allergic conjunctivitis, it is very rare to experience any serious complications. However, you may find your reoccurring symptoms frustrating. For example, if your conjunctivitis is caused by pollen, you may find it difficult to go outside during the spring and summer months without triggering your symptoms. This type of allergic conjunctivitis can affect your daily life and could make it difficult for you to concentrate at work or school, particularly if your eyes are severely irritated. Although this can affect your quality of life, it should not cause any long-term health problems.

4.14.1 VKC

Visual loss may be due to keratoconus and corneal scars, as well as complications of the

unsupervised use of topically administered corticosteroids.

4.14.2 GPC

Complications may arise if GPC is not treated. The complications could include:

- Prolonged discomfort, mental and emotional stress.
- Corneal damage, scar.
- Multiple damage to the eye conditions.
- Bacterial or viral (herpes simplex) infections can occur superimposed.

4.15 Prognosis

Since allergic conjunctivitis generally clears up readily, the prognosis is favorable. Complications are very rare, with secondary corneal ulcers or keratoconus occurring rarely. Although SAC, PAC, and GPC commonly reoccur, they rarely cause any visual loss. Conversely, VKC and AKC are frequently associated with significant risk of progressive corneal damage and resultant visual loss. In general, the prognosis of SAC and PAC is good despite significant discomfort and undesirable cosmetic consequences. Occasionally, individuals with chronic recurrences develop significant conjunctivochalasis or, less commonly, a corneal Dellen secondary to persistent limbal conjunctival chemosis. Conversely, AKC and VKC may lead to significant corneal complications such as ulceration and opacification, leading to permanent visual loss. Furthermore, significant chronic ocular surface disease places these patients at high risk for corneal transplantation complications and rejection. Lid involvement from any type of allergic conjunctivitis, particularly GPC, can significantly compromise contact lens tolerance. Medications used for allergic disease may lead to complications such as preservative toxicity and steroid-induced intraocular pressure (IOP) elevations or cataract. With proper treatment, you can experience relief or at least reduce your symptoms. Recurring exposure to allergens, however, will likely trigger the same symptoms in the future.

4.15.1 VKC

Generally, VKC is a rather benign and self-limiting disease that may resolve with age or spontaneously at puberty (Takamura et al. 2017; Takamura 2010). Nonetheless, the sometimes debilitating nature of this disease when it is active necessitates therapy to control symptoms. Complications typically arise from occasional corneal scarring and the unsupervised used of topical corticosteroids. In some patients, symptoms may persist beyond childhood, which in some cases may represent a conversion to an adult form of atopic keratoconjunctivitis. This persistence into adulthood has been shown to be as high as 12%.

4.15.2 AKC

AKC remains chronic for years, often persisting into old age, when it may resolve spontaneously. It may result in decreased vision or blindness from corneal complications, such as chronic superficial punctate keratitis, persistent epithelial defects, corneal scarring or thinning, keratoconus, cataracts, and symblepharon formation. Complications result from persistent surface keratopathy, corneal scarring or thinning, keratoconus, cataracts, and symblepharon formation. In addition, medical treatment with corticosteroids can further promote the development of cataracts, glaucoma, and secondary corneal infections. Proper prophylactic measures, prompt effective treatment of exacerbations, and well-timed elective surgical intervention can reduce the incidence of poor vision and blindness. Patients should be observed every few days or weeks until the ocular surface disease is stable. Moreover, when medically treating patients with steroids or immunosuppressants, a regular interval survey for drug-related adverse effects and complications is indicated. Patients should be observed frequently until the ocular surface disease is stable. Patients being treated with corticosteroids or

immunosuppressives should have regular examination for drug-induced adverse effects. Corticosteroids promote the development of cataract, glaucoma, and may lead to secondary corneal infections.

4.15.3 GPC

Functional prognosis of the GPC is good. Approximately, 80% of patients can return to comfortable contact lens wear with appropriate treatment. Ptosis of the upper lids and decreased contact lens tolerance can occur. Giant papillary conjunctivitis has been a common cause for temporary and permanent contact lens intolerance. The lids of some patients return to normal appearance following the resolution of giant papillary conjunctivitis, whereas other lids retain small, white, capped scars of the giant papillary lesions for long periods, sometimes indefinitely. Giant papillary conjunctivitis is not associated with mortality.

4.16 Home Care

Treating allergic conjunctivitis at home involves a combination of prevention strategies and activities to ease your symptoms. To minimize your exposure to allergens:

- Close windows when the pollen count is high.
- Keep your home dust-free.
- Use an indoor air purifier.
- Avoid exposure to harsh chemicals, dyes, and perfumes.
- To ease your symptoms, avoid rubbing your eyes.

Applying a cool compress to your eyes can also help reduce inflammation and itching.

Antigens flying into the ocular surface can be washed out by several drops of artificial tear. Because ordinary artificial tear contain preservatives, when instillation is repeated four or more times, an artificial tear without preservatives is recommended for safety. Since tap water reduces the stability of the layer of tears, frequent use of water for washing eyes should be avoided.

Cup-type eye washing tools are not recommended because skin blurs around the eyes and antigens attached to the skin touch the ocular surface. Furthermore, it pushes mites, bacteria, and other microorganisms spreading around the eyelids to the surface of conjunctiva and cornea. Such unsanitary and inappropriate cleaning operations are not medically recommended at all.

4.17 Prevention

Completely avoiding the environmental factors that cause allergic conjunctivitis can be difficult. The best thing you can do is to limit your exposure to these triggers. For example, if you know that you are allergic to perfume or household dust, you can try to minimize your exposure by using scent-free soaps and detergents. You may also consider installing an air purifier in your home. Early diagnosis and treatment will help prevent the rare complications that can occur with this disease.

4.17.1 SAC and PAC

Avoidance of the offending antigen is the primary behavioral modification; specific testing by an allergist, otolaryngologist, or eye care provider will identify the responsible allergen(s) and help the individual to establish a viable long-term strategy to avoid the allergen. Point-of-service 60-antigen regionally specific noninvasive fully reimbursable skin testing can readily be performed in the ophthalmologist's office, as well as the optometrist's office (in some states), with the Doctors Allergy Formula test kit (Bausch & Lomb), facilitating patient access and enhancing convenience. Contact reactions caused by medications or cosmetics are also treated best by avoidance.

4.17.2 VKC

As with most type I hypersensitivity disorders, allergen avoidance should be emphasized as the

first-line treatment. Although permanent relocation to a cooler climate is not feasible in many cases, it remains a very effective therapy for VKC. Maintenance of an air-conditioned environment and control of dust particles at home and work may also be beneficial. Local measures, such as cold compresses and periodic instillation of artificial tears, have also been shown to provide temporary relief. As with all allergic conditions, rubbing should be minimized through counseling, family engagement, cool compresses, chilled eye drops, and frequent handwashing to remove adherent pollen and bioadhesive allergens.

4.17.3 AKC

For optimal long-term prevention of AKC, reduce or eliminate the exposure to environmental allergen. The general principle for preventing all allergies is to avoid the triggers. Triggers for eye allergies can be avoided by (i) using sunglasses to act as a barrier for airborne allergens, (ii) using hypoallergenic bedding, (iii) washing sheets in hot water, and (iv) minimizing animal exposure, if animals are believed to trigger allergic symptoms. People who do not know what causes their allergic conjunctivitis may consider consulting an allergy specialist. The specialist may do allergy testing to find out what triggers the allergic symptoms. Mast cell stabilizers and antihistamines are the mainstay of prophylactic therapy. Reduction of environmental allergens along with oral and topical antihistamines helps in management of exacerbations.

4.17.4 GPC

Prevention of GPC involved reducing the possibility of getting your eyes irritated. If you are a contact lens wearer, the most important step of preventing GPC is to maintain the highest level of lens hygiene. Throw away whatever contact lenses you have been wearing as they may contain residues of the infectious agent. If disposing is impossible, disinfect them thoroughly using peroxide-based cleaning solutions and also some form of enzyme cleaning. Thoroughly clean and disinfect lenses between use. For soft lens wearers, use nonpreserved solutions when possible. Always rinse lenses in nonpreserved saline before inserting. Always remember wash your hands clean before handling contact lenses, and do remember to disinfect your lens storage also (Allansmith et al. 1977).

The goal of management is to allow the GPC patient to continue wearing contact lenses or to tolerate an ocular prosthesis with the benefit of the most effective and least obtrusive therapeutic program (Molinari 1982). Nonetheless, the treatment of GPC is complex, requires carefully sequenced clinical divisions, and can be both tedious and expensive for the patient and the physician. Six conditions favor the development or exacerbation of GPC: increased deposits on the lenses, increased time per day that lenses are worn, use of lenses consistently for months or years, individual reactivity to wearing a particular lens type, larger lens and therefore broader area of adhering antigenic material, and genetic constitution of the patient. The treatment of GPC depends on three therapeutic strategies: teaching the patient to clean the lens, finding the best tolerated lens, and treating the conjunctival inflammation.

4.17.5 Lens Care

Patients must clean the lens thoroughly, preferably using cleaning agents that are free of preservatives (e.g., thimersol). The lens should be rinsed and stored in fresh saline. Cold disinfecting solutions preserved with chlorhexidine should not be used. Three methods of sterilizing the lens are currently available: cold disinfection, heat disinfection, and treatment with hydrogen peroxide. In cold disinfection, the lenses remain overnight in the unheated disinfecting solution. Heat disinfection is effective, but the heat bakes the deposits on the surface of the lens. Hydrogen peroxide treatment depends on the disinfecting power of hydrogen peroxide, which is then neutralized by contact with a platinum disc. Of the three commercially available methods, treatment with hydrogen peroxide seems to be the best tolerated by the inflamed or potentially inflamed conjunctiva.

4.17.5.1 Deposits

Patients should clean their lenses with a proteolytic enzyme at least once a week. For some patients, daily cleaning with a proteolytic enzyme is recommended. Of the two enzyme preparations on the market – the proteolytic enzyme papain and a pancreatic enzyme containing lipases and proteolytic enzymes – the papain enzymatic cleaner seems to be more effective in removing deposits and quieting the GPC.

4.17.5.2 Type of Contact Lens

(i) Lens of the same design

In many patients, GPC can be controlled by reestablishing good cleaning practices, a new lens of the same design, and replacing the contact lenses every 6–12 months. The patient should then be instructed to clean the lens thoroughly and to use enzymatic cleaning as described above.

(ii) Lens of a different design

If proper care and cleaning of the lens and regular replacement do not resolve the GPC, a new contact lens of a different design should be prescribed. A lens of a different design and a polymer different from the one worn when the GPC developed (i.e., change manufacturers) should be prescribed. A lens of a lower water content also can be prescribed. We have initial evidence that non-hydroxyethylmethacrylate (HEMA) lenses may be better tolerated by patients with GPC than HEMA-containing lenses. Patients should be instructed to clean the new lens following the procedure described above.

(iii) Lenses of different design for each eye

A third maneuver in discovering a tolerable lens design is to prescribe lenses of different design for each eye. For example, one might prescribe a Hydrocurve lens for one eye and a CSI for the other, avoiding the polymer and design that had been associated with exacerbation of the GPC.

(iv) Rigid gas-permeable lens

A fourth option is to prescribe a rigid gas-permeable (RGP) lens rather than a soft (hydrogel) lens. RGP lenses are smaller and thus have less surface to hold deposits. The edge of a gas-permeable lens can be reshaped to be less traumatic to the conjunctiva. Finally, deposits are more easily removed from RGP lenses than from hydrogel lenses.

4.18 Current Research

Rebamipide acts by stimulating cells in the eye and altering the quality of the mucin or eye mucus which helps increase those cells known as goblet cells, to produce a more viable tear that protects the cornea (Kashima et al. 2014). Rebamipide eye drops attenuate giant papillae, suppress the inflammatory cytokines in human conjunctival epithelial cells, and downregulate the level of interleukin-8 (IL-8), eosinophil cationic protein (ECP), and total IgE level on the ocular surface in patients with allergic conjunctival diseases. Also another report investigate that the topical administration of rebamipide suppressed conjunctival allergic eosinophil infiltration in patients with allergic conjunctival diseases with giant papillae (VKC or AKC). These results revealed that the anti-inflammatory effects of rebamipide eye drops help to combat human ocular surface inflammation in patients with allergic conjunctival diseases. Moreover, rebamipide eye drops help in reducing the dependence on steroids for the treatment of allergic allergic conjunctival diseases.

4.19 Conclusion

Allergic conjunctival disease is defined as “a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective and objective symptoms.” Conjunctivitis associated with type I allergic reactions is considered allergic conjunctival disease even if other types of inflammatory reactions are involved. Classification of allergic conjunctival disease is as follows: (i) allergic conjunctivitis without proliferative change, (ii) atopic

keratoconjunctivitis (AKC) complicated with atopic dermatitis, (iii) vernal keratoconjunctivitis (VKC) with proliferative changes, and (iv) giant papillary conjunctivitis (GPC) induced by irritation of a foreign body. Allergic conjunctivitis is subdivided into "seasonal allergic conjunctivitis (SAC)" and "perennial allergic conjunctivitis (PAC)" according to the period of onset of the symptoms. The pathological conditions of allergic conjunctival disease with lesions in the conjunctiva are assumed to be caused by interactions between various immune system cells and resident cells, which are mediated by physiologically active substances (e.g., histamine and leukotriene), cytokines, and chemokines. Eosinophils are the main effector cells in allergic conjunctival disease. Various cytotoxic proteins released from eosinophils infiltrating locally into the conjunctiva are thought to cause keratoconjunctival disorders such as severe AKC and VKC. A clinical diagnosis can be made by subjective symptoms including ocular itching, lacrimation, hyperemia and foreign body sensation, and objective symptoms including conjunctival hyperemia, conjunctival edema, and conjunctival follicles, which are found annually during the same season. The most common and important symptom of SAC is the ocular itching. A positive test for serum antigen specific IgE antibody or a positive skin reaction, even in quasi-definitive diagnoses, makes it highly probable that a definite clinical diagnosis can be made. The serum total IgE antibody may be normal or mildly increased. The exposure to a large amount of antigens may induce acute bulbar conjunctival edema. Drug treatment is the preferred treatment for allergic conjunctival diseases. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. For severe allergic conjunctival diseases (AKC and VKC), additional use of immunosuppressive eye drops, steroid oral medicines, subtarsal conjunctival steroid injection, and surgical treatment such as papillary resection should be considered.

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