

OCULAR ALLERGY

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ABSTRACT

The eye is a common site of inflammation. Because the large majority of eye allergies involve the conjunctiva, the terms "ocular allergy", and "allergic conjunctivitis" are used synonymously. The clinical presentation of the various forms of allergic conjunctivitis can vary greatly, from mild symptoms unaccompanied by ocular signs, to severe disease with vision-threatening complications.

Although an IgE-mediated immediate hypersensitivity reaction has been demonstrated or postulated in many types, the pathophysiology underlying the allergic conjunctivitis is not fully understood. Great variety of available pharmacologic options is an evidence of the complexity of the chemical reactions associated with mast cell degranulation and mediator release causing the onset of allergic signs and symptoms.

After presentation of an actual case, this review provides an update on the various forms of ocular allergies focusing on the clinical features that help to differentiate different forms from each other and management.

INTRODUCTION

The term atopy, as first described by Cooch and Cooke (1), refers to allergic reactivity in persons with a hereditary predisposition who react to certain antigens scratched into their skin with a wheal and flare reaction. This reaction is mediated by IgE antibodies, fixed to the surface of mast cells leading to degranulation of the mast cells. The name atopy comes from the Greek word "atopos" meaning out of place. The major atopies include hay fever, asthma and atopic dermatitis. Minor atopic conditions are non-hereditary angioedema, idiopathic urticaria and food allergies.

Allergic disease is common, affecting 15% of the world's population; males are overrepresented in that number (2). Many of these patients also have eye disease ranging from mild seasonal allergic conjunctivitis to chronic vision threatening inflammation especially due to corneal involvement as in the cases of vernal or atopic keratoconjunctivitis.

There are 4 main types of allergic eye diseases: allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis. We herein discuss the clinical features, diagnosis and management of all these groups.

ALLERGIC CONJUNCTIVITIS

Seasonal (SAC) and perennial (PAC) allergic conjunctivitis are the most common forms of allergic conjunctivitis SAC representing approximately half of the cases of ocular allergy (3).

Symptoms include itching, burning, watery or sometimes mild mucoid discharge and usually bilateral (4). The conjunctivae are usually mildly injected and edematous leading to a "milky" appearance (Fig 1). Fine papillary hypertrophy of the upper tarsal conjunctiva may occur (5). Additionally the venous congestion can cause the appearance of dark circles around the eyes called "allergic shiner" (6). Many individuals also have concurrent nasal symptoms and because of the itchy nose they present a special habitus called "allergic salute" (Fig 2) (6). Corneal involvement is not among the findings. PAC is a variant of SAC that is chronic with year-round symptoms. In SAC the allergens are the pollens, and in PAC dust, mite feces, animal dander and feathers are the common antigens.



Fig. 1 Allergic conjunctivitis

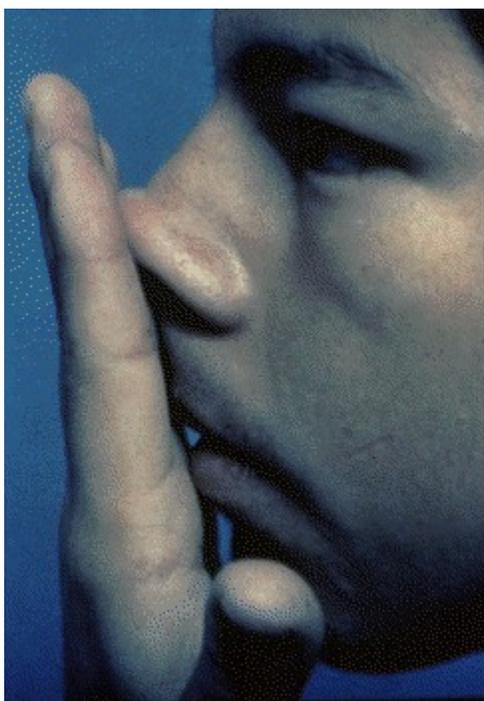


Fig. 2 Allergic salute

Pathophysiologic features of SAC and PAC are prototypic type I anaphylactic hypersensitivity reactions. In sensitized individuals the allergen crosslinks IgE antibodies on the surface of mast cells and basophils, resulting in the degranulation of these cells with release of mediators including histamine, prostaglandins, leukotrienes, and kinins. Patients with SAC and PAC have elevated levels of IgE in their tears and serum and pollen specificity has been demonstrated in both diseases (7).

Management begins with the avoidance of known allergens. Iced artificial tears or cold compresses may suffice to relieve mild symptoms. Pharmacotherapy is based on the severity of the clinical signs and symptoms. Topical antihistamines (e.g. pheniramine maleate, antazoline phosphate, pyrilamine maleate and levocabastine), usually in combination with decongestants (e.g. naphazoline) are the mainstay of the treatment. They have an immediate effect and exert their effect by competitively and reversibly blocking the receptors (8). Therefore they can be used on an "as necessary" basis. Topical non-steroidal antiinflammatory drugs (e.g. ketorolac tromethamine, flurbiprofen) inhibit the activity of cyclooxygenase pathway and therefore the production of the prostaglandins (9). They are especially useful for the vasodilatation and edema findings. Mast cell stabilizers (e.g. cromolyn sodium, nedocromil,

lodoxamide) act by preventing the calcium influx across mast cell membranes and therefore inhibit the degranulation (10). They also have some inhibitory effect on neutrophils and eosinophils. They should be used prophylactically and on a regular basis for effectiveness. In severe cases short term topical steroids may be considered, keeping in mind that long term use may be associated with cataracts, glaucoma, and superinfections of the ocular surface. In patients with significant nasal symptoms oral antihistaminics can also be used.

VERNAL KERATOCONJUNCTIVITIS

Vernal keratoconjunctivitis (VKC) is a chronic bilateral conjunctival inflammatory disorder typically affecting young males (11). The onset of the disease is generally before age 10; it lasts 2 to 10 years and usually resolves after puberty. The Mediterranean area and West Africa are the areas of the greatest numbers of patients. There is a history of eczema or asthma in 75 % of the patients (12). As the name implies, seasonal flare-ups are common, but patients usually have a year-round disease.

The "sine-qua-non" symptom of VKC is itching. Excessive tearing, ropy mucus production, photophobia, burning, foreign body sensation, pain are other common symptoms.

The signs are mostly confined to the conjunctiva and cornea. Eyelid skin and margins are relatively uninvolved compared to atopic keratoconjunctivitis. The "hallmark" finding of VKC is the cobblestone-like giant papillae of the upper tarsal conjunctiva (Fig 3). Bulbar conjunctiva is usually injected and edematous. Especially in heavily pigmented patients limbal changes are prominent. The limbus and perilimbal conjunctiva may be thickened and edematous forming a gelatinous-like hypertrophy. Limbal nodules and Trantas' dots composed of eosinophils and dead epithelial cells may be observed (Fig 4). Sometimes these limbal changes may result in pannus and superficial neovascularization of the cornea. Most important and vision threatening complications occur in the cornea usually in the form of mild epithelial keratitis or in more severe cases "shield ulcers". The characteristic shield ulcer of the VKC is typically oval or pentagonal, superficial, and superiorly located with grayish opacification of the bed and elevated margins (Fig 5) (13). Shield ulcer results from chemical damage to the epithelial surface by mediators released from mast cells and eosinophils. They are indolent and may take months to re-epithelize. In chronic advanced cases the inflammatory material is deposited in the form of opaque white or yellow "plaque".

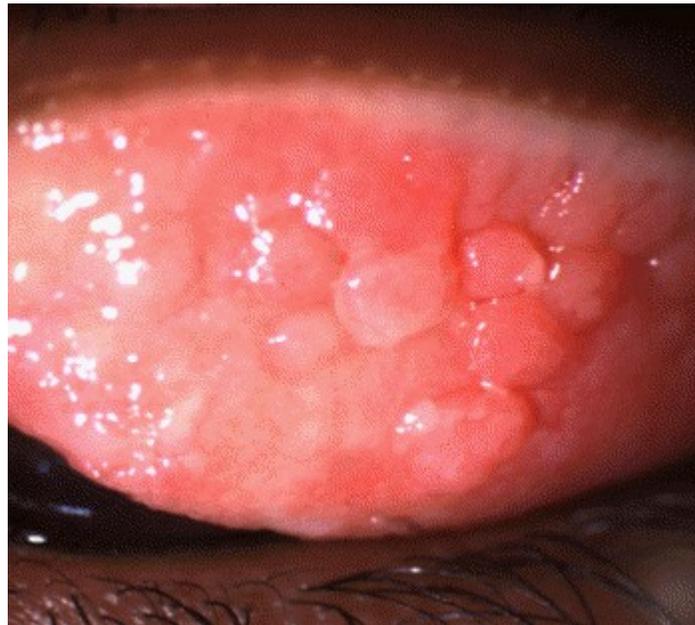


Fig. 1 Giant cobblestone papillae



Fig.4 Trantas' dots

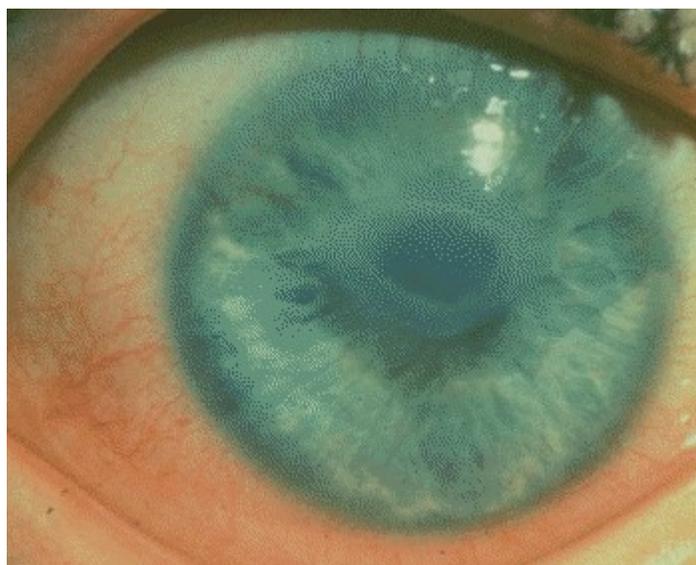


Fig. 5 Shield ulcer

In some cases, patients with VKC may resemble those with atopic keratoconjunctivitis (AKC). In AKC the eyelid inflammation and cicatrizing conjunctivitis, especially in the lower fornix leading to symblepharon formation, are pronounced, whereas in VKC these signs are not seen.

The etiology of VKC has been the subject of much speculation. Type I hypersensitivity probably plays a role in VKC, but other mechanisms, particularly type IV hypersensitivity, are also involved. The histopathology of the conjunctival papillae discloses not only the cells typically associated with allergic reaction (mast cells and eosinophils) but also large collections of mononuclear cells, fibroblasts and newly secreted collagen. It has been demonstrated that the conjunctiva of patients with VKC contains T-cell clones which are overwhelmingly CD4⁺ and secrete IL-4 but not gamma interferon after stimulation therefore being Th2 phenotype (14).

Although VKC is a self-limited disease, it is debilitating and may be sight threatening. Elimination of the allergens from the environment may be difficult, time consuming, and expensive; but it is a very important aspect in the long term control of the disease. Mast cell stabilizers are the mainstay of the pharmacological treatment. Since these agent have no effect on blocking the effects of released mediators, they should be used prophylactically before exposure to the antigen.

Corticosteroids inhibit phospholipase A2 hence the induction of the arachidonic acid cascade resulting in decreased capillary permeability and cellular exudation, blockage of the influx of leukocytes to the site of injury, and inhibition of fibroblast growth and release of hydrolytic enzymes from inflammatory cells (15). Topical steroids may be used in

the treatment of acute initial disease or to control breakthrough inflammation. But long term therapy should be avoided. Topical and oral NSAIDs may have beneficial additive effects in some patients. Topical cyclosporin 2% solution in olive oil has also been tried with promising results (16). Since it causes significant irritation and discomfort symptoms, patient compliance may be a problem. In severe vision threatening cases hospital admission and a course of oral steroids may be considered.

ATOPIC KERATOCONJUNCTIVITIS

Michael Hogan described atopic keratoconjunctivitis (AKC) in 1952 as an allergic keratoconjunctivitis occurring in association with allergic dermatitis (17). The reported incidence of ocular involvement in atopic dermatitis is 25 to 42% (18,19).

AKC most frequently occurs in men. It typically presents in the late teen years or early 20s, rarely before puberty, and may persist until the fourth or fifth decade of life. The incidence of AKC peaks in patients between 30-50 years (5).

Patients commonly complain of extreme itching, burning, and redness. There is usually copious mucous discharge gluing the eyes together upon awakening.

Eyelid disorders are the most common ocular complications of atopic dermatitis (19). Lids are often red, macerated with crusting and scaling (Fig 6), which are not seen in patients with VKC.



Fig. 6 Atopic blepharoconjunctivitis

Inferior forniceal conjunctiva is most commonly affected leading to symblepharon formation in severe cases. In some cases papillary hypertrophy of the inferior tarsal conjunctiva may occur, again differentiating it from VKC.

Punctate epithelial keratitis is an early corneal finding which may progress into persistent epithelial defects. These defects are often complicated by herpes simplex or staphylococcus aureus superinfections (19). Neovascularization of the cornea is seen in more severe cases (Fig 7). Keratoconus, retinal detachments and posterior subcapsular cataracts even in the absence of prior steroid treatment may be associated with this condition (19,20,21).

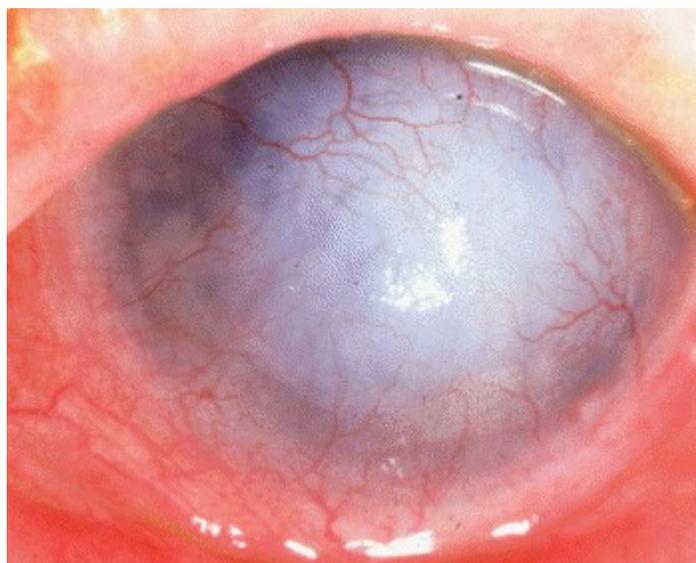


Fig. 7 Corneal neovascularization

Atopic individuals have a defect in suppressor T cells responsible for regulating IgE production to allergens. Type I hypersensitivity is only one of the mechanisms in the pathogenesis of AKC. Some of the immunopathological characteristics of AKC specimens are similar to those of cicatricial pemphigoid and ocular rosacea emphasizing that fibroblast activation, proliferation and production of cicatrization may result from a variety of chronic conjunctival inflammatory disorders in which T cells, macrophages and mast cells collaborate (22). The histopathologic findings of the conjunctiva of patients with AKC is quite peculiar characterized by mast cell and eosinophil invasion of the epithelium, epithelial pseudotubule formation and increased goblet cell presence. Mast cells and eosinophils along with a chronic mononuclear cell infiltration are also prominent in the substantia propria (22).

The goals of the treatment are to maintain the visual acuity and relieve patient symptoms. Patients suffer from a systemic disorder with ocular complications. Therefore, help of a clinical allergist and environmental control are the essentials of the management. Topical antihistaminics with vasoconstrictors and NSAIDs may help in relieving the symptoms in mild cases, and in acute exacerbations combined with other medications. Topical mast cell stabilizers are effective in the long term control of the ocular inflammation (23). Topical steroids may be considered in lid disease or in the case of vision-threatening corneal involvement. But prolonged use is not desirable because of associated side effects. In patients with significant skin findings or asthma, oral antihistaminics and NSAIDs may be used.

Cyclosporin A (CsA) inhibits the clonal expansion of T helper lymphocytes through inhibition of interleukin-2 production. Systemic CsA, 5 mg/Kg/day was found to be highly effective in patients with severe atopic dermatitis (24). Patients should be monitored closely to detect any systemic side effects.

Secondary cicatricial lid position abnormalities and trichiasis may require special surgical techniques for correction. When corneal scarring is profound, after quieting down the inflammation, visual rehabilitation with a corneal graft may be considered. However, in the post operative period many complications and suboptimal outcomes should be predicted (25).

GIANT PAPILLARY CONJUNCTIVITIS

Giant papillary conjunctivitis (GPC) is a well known complication of contact lenses, but has also been seen in patients after cataract surgery, ocular prosthesis, extruded scleral buckle, and corneal foreign bodies (26).

Although originally described as papillae on the upper tarsal conjunctiva 1 mm or larger in diameter, it is now believed that papules 0.3 mm or larger, in association with the symptom complex of itching, contact lens intolerance or conjunctival injection, meet the criteria for the diagnosis of GPC (27).

Patients complain of lens intolerance, excessive mucous secretion, blurred vision, itching, and ocular irritation. The giant papillae can be best seen after instillation of 2% fluorescein into the cul-de-sac and cobalt blue slit lamp illumination (Fig 8). The large papillae in the medial and lateral aspects of the upper tarsus and the ones along the tarsal border should not be used in evaluation as they may be seen in many normal individuals.



Fig. 8 Giant papillary conjunctivitis

Histopathology of the conjunctiva overlying the giant papillae demonstrates thickened and irregular epithelium, with many indippings to the underlying stroma. The epithelium over the atypical portions of the papillae may show localized reduction of the goblet cell population, whereas in the interpapillary crypts, mucus secreting elements seem to be hyperplastic. Keratinization of the upper tarsal conjunctiva has not been observed (28). Like in VKC or AKC, there are mast cells, eosinophils and basophils in the epithelium and substantia propria of the conjunctiva (28,29).

The etiology of the GPC is still not fully understood. Two possible theories include the type IV hypersensitivity reaction against the contact lens material itself, coatings of the lens, or lens solutions (27), and irritation due to the trauma to the tarsal conjunctiva with release of neutrophil chemotactic factor and other inflammatory mediators (30). Mostly accepted belief is the combination of the two occurring in the presence of atopic tendency.

Giant papillary conjunctivitis is somewhat less of a problem as it is non-vision-threatening. When the underlying condition is a suture or a foreign body, removal will be enough to improve patients' symptoms and signs. In contact lens wearers, treatment should be directed firstly to modify the patients' routine behavior, and often the lens itself. Improving the lens hygiene, finding a better tolerated lens design and material may be useful. Topical mast cell stabilizers have been reported to be helpful in patients with mild to moderate GPC (31). In severe cases, discontinuation of the lens may be necessary. Steroid use is not recommended because of the chronic nature of the condition.

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