VERNAL KERATOCONJUNCTIVITIS: A REVIEW
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ABSTRACT: Vernal keratoconjunctivitis (VKC) is a recurrent seasonal disease of childhood, characterized by severe bilateral inflammation of the conjunctiva and by giant papillae of the superior tarsal conjunctiva, gelatinous hypertrophy of the limbus, and keratopathy. Clinical and immunohistochemical studies suggest that IgE-dependent (type I allergic) and IgE-independent (type IV allergic) mechanisms are involved in the immunopathogenesis of VKC, in which various inflammatory cells, including different T cell subpopulations play an active role via a cascade of chemical mediators. Endocrine, genetic, neurogenic, environmental and socioeconomic risk factors have been identified. The clinical course of this disease is usually benign and self-limiting, but a minority of patients will face very debilitating and sight threatening complications. The variety of currently available drugs to treat VKC include anti-histamines, mast-cell stabilizers, dual acting agents, corticosteroids and immunomodulators but none is enough to treat all aspects of the multifaceted pathophysiology of VKC. More selective drugs like anti-chemokine receptor antibodies and leukotriene receptor antagonists are under evaluation. Cyclosporine has been shown to be effective in the treatment of VKC but further randomized control trials are required to establish the minimum effective concentration. The purpose of this paper is to describe the clinical expression of VKC, to discuss its pathogenic mechanisms, and to suggest novel therapeutic strategies.

KEYWORDS: Vernal Conjunctivitis, Mast Cell, Giant Papillae, Allergic Conjunctivitis.

INTRODUCTION: Vernal keratoconjunctivitis (VKC) is a severe perennial form of allergic conjunctivitis involving the cornea and conjunctiva.¹ The majority of patients are boys, with a (male: female) ratio of 3:1. The disease usually begins at the age of 6–10 years.² The condition usually resolves spontaneously by puberty, but if it does persist, the sex distribution equalizes.³ VKC usually has early onset and high clinical Morbidity.⁴ The condition is found commonly in atopic individuals, who may also suffer from eczema, asthma, or hayfever.¹

The prominent symptom is intense pruritis. Other complaints include photophobia, burning, tearing, mild ptosis, and a thick, ropy, yellow, mucoid discharge.⁵ Greater prevalence of VKC is seen in the regions with hot, humid climate, and higher load of airborne allergens. It is a common ocular surface disorder in the Mediterranean region, central Africa, India, and South America.⁶ It was first mentioned in the ophthalmic literature as conjunctiva lymphatica more than 150 years ago.

Subsequently, most of the ophthalmologist during that period (Arlt, Dasmarrres, von Graefe, Axenfeld, Trantas and Herbert) published about this interesting malady. Different authors, at different times, described it as spring catarrh, phlyctenula pallida, circumcorneal hypertrophy, recurrent vegetative conjunctiva, verrucosa conjunctiva and aestivale conjunctiva, calling attention to the various aspects of this disease. Although the allergic nature of this entity has been accepted for a long time, its exact etiology and pathogenesis is still unclear.
Recently, many clinical and experimental studies about the cells and the mediators involved in initiating and perpetuating ocular allergic inflammation have broadened our knowledge about the pathophysiology of this disease. The accumulation of a large amount of immunological data has established that the pathogenesis of VKC is much more complex than a mere type 1 hypersensitivity reaction.

To the present day, the precise role played by genetic predisposition and environmental factors in the onset, progression and resolution of this self-limiting, but at times incapacitating, childhood entity is an enigma. Despite the universal acceptance of the nomenclature vernal keratoconjunctivitis, occurrence of this disease is not limited to spring, with episodes of reactivity being quite common in the winter.

The initial seasonal attacks turn into perennial disease after a few years. The efficiency of school-aged children decreased profoundly because of the chronic and recurrent course. Although this is not usually a blinding disease, visual impairment may occur if the cornea is involved.7

Clinical Features: The three forms of the vernal conjunctivitis are palpebral, limbal, and mixed. The palpebral form is marked by cobblestone papillae on the superior tarsal conjunctiva while the lower lid is minimally affected. The initial change is papillary hypertrophy, after which the connective tissue of the substantia propria undergoes hyperplasia and proliferation to form giant papillae that can reach up to 7–8mm in diameter. Giant papillae are one of the hallmarks of the disease.5

Giant papillae [Fig. 1] consist of a papillary conjunctival mass >1 mm in size on the tarsal conjunctiva, with a proliferation of collagen underneath the conjunctival epithelium. The presence of giant papillae signifies prolonged chronic inflammation, and conjunctival fibrosis can occur in the long term. The presence of giant papillae indicates poor prognosis of the disease.8

The pressure of the cornea flattens the tops of the giant papillae to produce a pattern that resembles cobblestones. Tiny twigs of vessels are found in the centers of the papillae, which helps to differentiate these from large follicles such as may be seen in trachoma. When wiped with a cotton-tipped applicator, a milky veil that overlies the cobblestones pulls off in a stringy fashion.5

The limbal form is marked by a broad, thickened, gelatinous opacification of the superior limbus [Fig. 2] that can override the cornea. Again, tiny, twig-like vessels arise in the centers of these rounded lumps, whereas in limbal follicles the vessels appear around the sides of the elevations. Histologically, the tissue is infiltrated with lymphocytes, plasma cells, macrophages, basophils, and many eosinophils.

A characteristic manifestation of limbal vernal conjunctivitis is the presence of Horner-Trantas dots, which are white, chalk-like dots composed of eosinophils and epithelial debris located at the limbus.5 Trantas dots tend to appear when VKC is active, and disappear when symptoms abate.9

The cornea can be involved in up to 50% of cases. Corneal manifestations include a superficial pannus and a punctate epithelial keratitis. Small, gray patches of necrotizing epithelium may involve the upper one third to two thirds of the cornea – in severe cases, the cornea appears to be dusted with flour. The affected area stains with fluorescein.

A vernal “shield ulcer” [Fig. 3] develops as a horizontally oval, shallow, non-vascularized, indolent ulcer of the superior cornea that leads to severe discomfort. The edges are composed of shaggy, gray, dead epithelial cells, and there is infiltration of the underlying superficial stroma.
After the ulcer heals, a mild corneal opacity may persist at the level of Bowman's layer. Pseudogerontoxon, which resembles arcus senilis, is a waxing and waning grey-white lipid deposition in the superficial stroma of the peripheral cornea. Ocular complications of VKC have been reported to include steroid-induced cataract and glaucoma, corneal scarring, microbial keratitis and limbal tissue hyperplasia. Amblyopia seen among VKC may be caused by corneal opacity, irregular astigmatism and keratoconus. Dry eye syndrome, reported in patients suffering from VKC, may be caused by unsupervised use of topical corticosteroids.

**PATHOGENESIS:** Vernal keratoconjunctivitis has mixed features and stages of acute and chronic ocular inflammatory conditions, IgE-mediated hypersensitivity and T cell–mediated responses and reactions are both involved. On the basis of challenge studies as well as immunohistochemical and mediator studies, a Th2-driven mechanism with the involvement of mast cells, eosinophils, and lymphocytes has been suggested. Th2 lymphocytes are responsible for both hyper production of IgE (interleukin 4, IL-4) and for differentiation and activation of mast cells (IL-3) and eosinophils (IL-5).

Other studies have demonstrated the involvement of neural factors such as substance P and NGF in the pathogenesis of VKC, and the overexpression of estrogen and progesterone receptors in the conjunctiva of VKC patients has introduced the possible involvement of sex hormones. Thus, the pathogenesis of VKC is probably multifactorial, with the interaction of the immune, nervous, and endocrine systems.

**Mediators in VKC:** The plethora of mediators and cytokines in VKC compared to controls, seasonal allergic conjunctivitis and giant papillary conjunctivitis provides a new perspective on the complex inflammatory processes occurring on the ocular surface in this chronic disease.

**Cytokines:** Cytokines are small secreted proteins that mediate and regulate immunity and inflammation. Two distinct subtypes of helper T cells produce different cytokines. T cells isolated from conjunctiva of VKC patients and expanded into cell lines showed a Th2-like cytokine profile. Th2 cytokines, i.e. IL-4 and -5, were high among VKC patients. The serum levels of IL-4 and tear levels of IL-4, 5 were higher in patients with VKC compared to controls. Interestingly, IL-2, interferon (IFN)-gamma and tumor necrosis factor (TNF)-b, the major cytokines secreted by Th1, was not increased in VKC. These findings confirm that VKC has a mainly Th2 Profile.

**Chemokines:** Recently, a family of chemoattractant peptides, termed chemokines, has been recognized to have an important role in normal leucocyte trafficking as well as in leucocyte recruitment during inflammation. In addition to cell movement, chemokine receptor signaling activates gene expression and can induce intracellular events, such as mast cell degranulation. IL-8 and the CXC chemokine, monokine induced by interferon gamma (Mig), seem to play an important role in the pathogenesis of VKC. The chemokine IL-8 actively secreted by macrophages and epithelial cells in VKC is a chemoattractant as well as an activator of polymorphonuclear cells. It plays a crucial role in inflammatory cell migration.

More polymorphonuclear cells and eosinophils have been correlated with increased IL-8 concentrations. Chemokine receptor (CXCR)-3 is greatly upregulated and expressed abundantly on T lymphocytes in the conjunctiva of patients with active VKC.
Over-expression of this receptor and chemokine Mig may play an important role in the regulation of lymphocyte recruitment within them conjunctiva of VKC patients.7

**Histamine:** Histamine, an important inflammatory mediator in allergic eye disease, is released by activated mast cells and basophils. Tear concentration of histamine was higher in VKC patients compared to normal volunteers and other inflammatory eye diseases. Persistent elevation of histamine levels in VKC tears is probably caused by its reduced inactivation by histaminases13 and increased production by specific or non-specific activation of mast cells and basophils. Patients affected with VKC demonstrate a non-specific conjunctival hyper-reactivity to histamine.7

**Metalloproteinases (MMPs):** Metalloproteinases (MMPs) are extracellular endopeptidases that selectively degrade components of the extracellular matrix. Inflammatory cells, particularly eosinophils, and structural cells like epithelial cells and conjunctival fibroblasts are the probable cellular source of these enzymes.7 Laminin and tenascin facilitate the transmigration of inflammatory cells into the conjunctiva via their adhesive properties and induce matrix metalloproteinases (MMPs) such as gelatinase B, that disrupt the integrity of the ECM, allowing invasion of inflammatory cells and contributing to tissue remodeling.14

MMP enzymes are inactivated by tissue inhibitors of MMPs (TIMP-1). Increased levels and activity of MMP and an imbalance between MMPs and TIMP may be involved in the pathogenesis of VKC. Tear levels of pro-MMP-1 and pro-MMP-9 were significantly increased in patients with VKC compared to control subjects. MMP-9 activity correlated significantly with corneal involvement and giant papillae formation.7

**Cells in VKC:** Mast cells, T cells, eosinophils and macrophages are seen in increased numbers among VKC patients.

**Mast cell:** The mast cells are the key cellular component and play a pivotal role in initiating the inflammatory cascade in allergic eye disease. Mast cells express Fc [epsilon] RI on their cell surface, which enables them to bind IgE. The cross-linkage of this IgE by specific allergens results in the release of pro-inflammatory mediators, including histamine, proteases, prostaglandin D2 and leukotriene C4, into the local extracellular environment.7

A comparison of the percentage of degranulated mast cells in VKC and GPC showed little difference. The fact that histamine levels are dramatically elevated in VKC and not in GPC suggests that there is a higher level of histamine release from the mast cells of patients with VKC.13 Vasodilation, chemosis and itching of eye are caused by histamine interaction with H1 receptors.

It has been shown that mast cells in conjunctiva can synthesize IL-4. Mast-cell cytokines are responsible for the initiation of allergic inflammation, resulting in eosinophil infiltration associated with vernal conjunctivitis. IL-4 plays a key role in allergic inflammation by promoting T cell growth, induction of IgE production from B cells, up regulation of adhesion molecules and regulation of Th2 subset differentiation, which is essential for the allergic reaction. Furthermore, IL-4 is reported to induce eotaxin production in keratocytes, which may promote eosinophil recruitment to corneal ulcer.7
Eosinophils: Eosinophil recruitment to the conjunctiva is thought to play a central part in the pathophysiology of VKC. Activated eosinophils release strong basic cytotoxic proteins such as major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophils derived neurotoxin which are released in the conjunctiva and tear fluid and damage the conjunctival and corneal epithelium.\(^\text{11}\) The mucoid plaque overlying the shield ulcer has been shown to contain eosinophils and their granules.\(^\text{13}\) The selective recruitment of eosinophils to sites of inflammation is controlled by cytokines, and adhesion molecules.\(^\text{11}\)

T cells: Th2 lymphocytes, by virtue of their cytokine profile, are responsible for increased production of IgE, recruitment and activation of mast cells and eosinophils. These T cells actively interact with other inflammatory cells, such as macrophages. Intercellular adhesion molecule-1 (ICAM-1), CC chemokines, macrophage-derived chemokine, E-selectin and human leukocyte antigen DR (HLA-DR), over-expressed in VKC and acting concomitantly, may be responsible for the recruitment and activation of helper T cells in VKC.\(^\text{7}\)

Conjunctival Epithelial Cells: Apart from acting as simple physical barrier to the entrance of foreign invaders, ocular surface epithelium is actively involved in the initiation and continuation of the allergic inflammatory process.\(^\text{15}\) The epithelium is stimulated by inflammatory molecules, such as histamine, to express intercellular adhesion molecules (ICAM-1) and to secrete inflammatory cytokines and chemokines.\(^\text{14}\)

Fibroblasts: It has been shown that corneal and conjunctival fibroblasts not only maintain tissue structure but also contribute to the induction and amplification of ocular allergic inflammation as well as tissue remodeling.\(^\text{7}\)

Treatment: Therapy for VKC, should be aimed primarily at the identification of the allergen and, when possible, its elimination or avoidance. Tear substitutes are helpful because of their barrier function, their allergen dilutional function, and their irritating ability. The use of vasoconstrictors can inhibit vascular transudation, thus decreasing chemosis. Although rebound vasodilatation does not occur with the ocular use of vasoconstrictors, overuse must be avoided to prevent tachyphylaxis and medicamentosa.\(^\text{13}\) Topical antihistamines, such as levocabastine and emedastine alleviate ocular allergy quickly by binding to histamine receptors but are only effective in mild cases.\(^\text{14}\)

Drugs, such as sodium cromoglycate, nedocromil sodium, pemirolast, and lodoxamide act by stabilizing mast cells. These therapeutic agents prevent the mast-cell degranulation process and eventually inhibit the inflammatory cascade in allergic conjunctivitis.\(^\text{15}\) Dual action agents such as olopatadine and ketotifen combine the best of both worlds by their immediate histamine receptor antagonism, coupled with the long-term disease-modifying effect of mast cell stabilization.\(^\text{14}\)

Olopatadine 0.1\% has also been shown to reduce the number of goblet cells in brush cytologic specimens of VKC patients after 2 months of treatment, which, in turn, decreased the amount of mucus discharge.\(^\text{13}\) Non-steroidal anti-inflammatory drug (NSAID) topical agents reduce ocular inflammatory signs by inhibiting cyclooxygenase and have a beneficial effect on the course of VKC reducing the local steroid needs. Careful follow-up is needed, since corneal melting has been reported after instillation of several types of topical NSAID.\(^\text{14}\)

The double-edged sword of steroids is acutely evident in VKC therapy. Therapeutic response to topical steroids can be dramatic. However, the potential for super infection and delayed wound
healing as well as cataract and glaucoma development must be taken into account. For these reasons, pulse therapy of a topical steroid such as prednisolone phosphate 1%, six to eight times per day for up to 1 week, followed by rapid tapering to the lowest levels needed for patient functioning, should be prescribed.13

Corticosteroids like hydrocortisone, triamcinolone, clobeta-sonebutyrate, fluromethalone, rimexalone, prednisolone, dexamethasone have been widely used in the treatment of allergic conjunctivitis.15 Steroids should not be used to eliminate the last vestige of vasodilatation or itching, nor should the clinician expect immediate resolution of the cobbles. Supratarsal injection of steroid has been used with success in severe cases of VKC. However this is an invasive procedure and there is a risk of developing glaucoma or/and cataract.13

Immunomodulatory agents are the substances that interact with immune system. These compounds cause immunostimulation and immunosuppression. Immunomodulatory agents are associated with fewer side effects. Hence, these compounds are preferred over corticosteroids in the treatment of allergic conjunctivitis. Several immunomodulatory agents such as cyclosporine A (CsA), tacrolimus (FK 506), mycophenolate mofetil (MMF), leflunomid, rapamycin (sirolimus), capoxone, laquinimod, infliximab have also shown efficacy in the treatment of ocular immune-mediated diseases.15

The management of vernal keratoconjunctivitis is determined by the severity of the disease. A step ladder pattern of treatment [Fig. 4] should be followed. Mast cell stabilizers are effective in mild disease (symptoms with conjunctival involvement alone). In patients with moderate disease (papillae or limbal inflammation with punctate erosions) with intermittent or seasonal episodes, mild steroids are safe to use, however if the disease is chronic, cyclosporine drops (0.5–2%) may be steroid sparing and safer for long-term management.

In patients with severe disease (cobblestone papillae or limbal deficiency with coarse erosions or shield ulcers) potent steroids are indicated in addition to mast cell stabilizers, lubricants and cyclosporine. Though effective, side effects restrict their long-term use. Patients with refractory severe disease or vision-threatening allergy may benefit from systemic immunosuppressive therapy.

Oral steroids are very effective; however, if required repeatedly second line immunosuppressives may be agents of choice. Guidelines regarding systemic immunosuppressive therapy are not available in the literature except for an isolated case report of immunoglobulin therapy.16

![Figure 4: Image showing step ladder pattern of treatment](image-url)
Surgical Treatment: Cobbles can remain for many months without creating clinical problems. Surgical removal of these cobbles with cryotherapy should be avoided, because the resultant scarring of the conjunctiva can lead to lid and tear film abnormalities that will persist as a life-long problem after the VKC has spontaneously resolved. Patching with antibiotic-steroid combinations is highly effective in treating shield ulcers, and in recalcitrant cases of shield ulcer plaque, debridement is highly effective with or without amniotic membrane.\textsuperscript{13}

Excimer laser phototherapeutic keratectomy helps in early re-epithelialization of vernal shield ulcer refractory to medical treatment. Free autologus conjunctival graft after resection of giant papillae facilitates the re-epithelialization of non-healing shield ulcer. Cultivated corneal epithelial cells could be transplanted to treat the severe ocular surface diseases associated with VKC. Vision improves significantly after transplant. Corneal epithelial cell transplants could be beneficial when amniotic membrane transplant is not sufficient to restore the ocular surface.\textsuperscript{7}

Recent patents on treatment of allergic Conjunctivitis: A recent invention discloses a method of treating conjunctivitis by administrating lipid-conjugates claimed to suppress the expression of PLA2 enzyme and therefore can be used to suppress, inhibit and prevent pathologic conditions associated directly with conjunctivitis and also reduce the symptoms. Chlorogenic acid and its ester derivatives produce an inhibitory effect on transglutaminase and are highly effective in the treatment of conjunctivitis through anti-inflammatory effects.

Another patent disclose a pharmaceutical composition comprising of aqueous solution of epinastine for topical administration which prevents occurrence of Late phase response thereby provides long lasting effect in the treatment of allergic conjunctiva. TLR antagonist or TLR-coreceptor antagonist that prevents the binding of pathogenic ligands to the TLR or coreceptors and generates anti-allergic activity.

The inventors disclosed many compounds with anti-allergic effects including oligodeoxynucleoside, antihistamines, leukotriene antagonists, mast cell stabilizers, immunomodulators, anti-IgE agents, a ligand of Vit D receptor, an antimicrobial agent, a quinazoline derivative or an antibody that inhibits the activity of TLR.

Another patent application has disclosed a class of pyrimidine derivatives that act on TLR7 for the treatment of viral or allergic diseases and cancers. A novel target spleen tyrosine kinase (Syk) which regulates the phosphorylation of enzymes such as phopholipase-C, phosphotidylinositol-3 kinase and protein kinase which regulate the release of histamine. The inventors have filed another patent for the use of medicament containing interfering RNA that targets histamine receptor H1 (HRH1) mRNA.\textsuperscript{15}

Future of vkc pharmacological Therapy: Despite the development of newer drugs in the last decade, the statement of Professor Lightman – “at present however, the current situation for those with severe VKC remains a disturbing dependence upon topical steroids, with all the attendant risks”, emphasizing the need for more selective drugs for better and long-lasting control of VKC– is still appropriate.\textsuperscript{7}

Antichemokine receptor antibodies inhibit eosinophil chemotaxis. Inhibition of CC chemokine receptor-3 may be a treatment for corneal ulceration in patients with VKC. Several steps can be targeted in the design of such drugs: the chemokines themselves (Both before and after synthesis),
their receptors, chemokine signaling, and perhaps intracellular mechanisms of leukocyte movement. So far, results with topical cyclosporine are very encouraging but because of unavailability of commercial preparations of topical cyclosporine in higher concentrations, its use in VKC is limited.\(^7\)

Another novel drug mycophenolic acid inhibit T and B lymphocyte replication and recently under investigation for the conjunctivitis therapy. Another target Janus protein kinase-3 is involved in the activation and proliferation of T-cells.

Future drug design approach would be based on evaluating novel inhibitors of JAK-3 which may be an effective therapy for AKC and VKC. A study also suggests the application of monoclonal antibody i.e. the humanized anti-eotaxin 1 for the inhibition of human conjunctival mast cell by acting on eotaxin receptor. Monoclonal antibody based therapy can be explored further to evaluate its potential in the treatment of allergic conjunctivitis. Therefore, development of novel drug molecules will be a valuable tool in the treatment of allergic conjunctivitis.\(^15\)

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