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Review Article

Immunology of vernal keratoconjunctivitis

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ABSTRACT

Vernal keratoconjunctivitis (VKC) is a bilateral seasonally occurring chronic inflammation of the conjunctiva especially in the adolescent boys, the pathogenesis of which includes a variety of genetic, climatic and environmental factors. The symptoms include itching, photophobia, watering and redness, ropy discharge which eventually lead to punctate epithelial erosions, shield ulcers over corneal and affects the vision and quality of life of young children. There are three types of VKC- palpebral, bulbar and mixed forms. The palpebral form has cobble stone papillae and congestion. The bulbar form shows horner tranta spots and pseudogerontoxon, while the mixed form has both. Several cells like histamines, IgE, chemokines, lymphokines play a role in the pathogenesis of the disease. The aim of this review was to review article of the multitude of cells and mediators that have a relevant role in VKC and the necessary treatment options targeted against the specific cells that may help in subsiding the disease process.

Keywords: Vernal keratoconjunctivitis, Allergic conjunctivitis, Cytokines, IgE

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a bilateral seasonally occurring chronic inflammation of the conjunctiva. According to the clinical manifestations, course, and prognosis differences, it is classified under one umbrella term called allergic conjunctivitis which also includes perennial and seasonal allergic conjunctivitis (PAC, SAC), atopic keratoconjunctivitis, and giant papillary conjunctivitis (GPC). VKC is more frequent in the Mediterranean area, central Africa, Japan, India, and South America but is also reported in North America, China and Australia, Great Britain, and Sweden. The pathogenesis includes a variety of genetic, climatic and environmental factors. However, though the relationship of VKC with a particular genotype has not been confirmed yet, studies suggest that it may be a phenotypic model of up regulation of the cytokine gene cluster on chromosome 5q. VKC occurs more during spring and summer predominantly in young males and these patients are prone to have a family history of allergic diseases like asthma, rhinitis, eczema, urticaria, and dermatitis.[1]

CLINICAL FEATURES

Itching, photophobia, burning, excess mucus and tearing are the major ocular symptoms. Corneal involvement may occur and result in permanent vision damage. Patients also complained of frequent conjunctival redness after exposure to nonspecific stimuli possibly due to the release of vasoactive mediators.[2] There are 3 types of VKC. The palpebral form is associated with a hypertrophic tarsal response in the form of papillae, giving it the characteristic 'cobblestone appearance' constituting from the vasculostromal structure of collagen types I and II and proteoglycans while the limbal form consists of diffuse thickening of the limbal tissue (usually at the superior limbus) and Horner trantas spots. The mixed type presents intermediate characteristics between the two.[3] Hypertrophic limbal masses and pseudoepitheliomatous

hyperplasia resembling OSSN are relatively uncommon.[4] Interestingly, limbal patients more frequently prove negative to skin or serum specific IgE tests than tarsal VKC patients. Eye rubbing and activation of metalloproteinases may play a role in the development of keratoconus in VKC.

IMMUNOLOGY

VKC is traditionally thought to be an allergic disorder in which an IgE-mediated anaphylactic hypersensitivity is one of the essential pathogenic mechanisms. Nevertheless, the commonly observed lack of IgE specific sensitization suggests that a cellular hypersensitivity may also be involved in VKC pathogenesis. Cytological, biohumoral, immunohistological, and molecular biological studies indicate that VKC is a Th2 lymphocyte-mediated disease.

A multitude of cells and mediators have been detected in the serum, conjunctiva, and tears of patients with VKC, which may have a relevant role in the pathogenesis of the disease.[1]

IgE

An exclusively local hyper production of IgE, confirmed by the finding of specific IgE only in tears and a positive SPT was shown only in 30 to 50% of VKC patients unlike SAC or PAC which are mainly dependent on classical type I hypersensitivity in which patients have positive skin prick tests and specific IgE in serum to airborne allergens.[1,3]

Lymphocytes

The conjunctival accumulation of Th2 lymphocytes, which mediate many of the histopathological changes seen in allergic diseases by producing IL-3, IL-4, IL-5, IL-10, IL-13, and GM-CSF, confirms that VKC is an allergic disorder. The imbalance between Th2 and Th1 lymphocytes is responsible for an over activation of Th2 cells, giving rise to a hyper reactivity against substances that commonly come in contact with the mucosa. This may in part explain the disease exacerbations after exposure to environmental factors, such as wind, sun radiation, and hot weather conditions. Th2-derived cytokines favour a local hyper production of IgE (IL-4, IL-9, IL-13), an increased number of eosinophils (IL-5, GM-CSF) and mast cells (IL-3), and the continual activation of both.

Th2 lymphocytes and increased levels of Th2-type cytokines were found in both tarsal and limbal patients with either positive or negative specific IgE allergy test results. This signifies that Th2 and Th2-type cytokines are essential for the development of the disease and that IgE is not. In fact, IL-4 or IL-13 expression and production were not always identified in VKC patients, explaining the lack of IgE switching in the course of a Th2-mediated reaction.[1]

Mast cells

Activation of mast cells by either IgE mechanism, specific or nonspecific stimuli is the crucial mechanism in triggering the allergic reaction (through the release of histamine) and the recruitment of inflammatory cells (lymphocytes and eosinophils). Tryptase is a neutral protease and is a specific marker of mast cell activation. It may activate other proteases, like matrix metalloproteinase (MMP), and probably involved in extracellular matrix degradation and inflammatory cell infiltration.[1]

Histamine

Histamine is the classic mediator of allergic disease and accounts for 98% of the mast cell granules content. Chronic eyelid rubbing in cases of VKC, even in the absence of stimulation was shown to be associated with a defect in the activity of the histamine-metabolizing enzyme, histaminase. Histamine also stimulates conjunctival fibroblasts, increasing the production of procollagen I and proinflammatory cytokines, highlighting its role in the tissue remodeling and collagen deposition in VKC tissues.[1]

Eosinophils

In allergic conjunctival inflammation, eosinophils can be locally activated by specific allergens through IgE receptors and by nonspecific stimuli, subsequently releasing proinflammatory mediators (leukotrienes, prostaglandins, platelet-activating factor, etc) and toxic factors, such as major basic protein, eosinophil cationic protein (ECP), eosinophil peroxidase, and eosinophil neurotoxin which are probably responsible for the corneal epithelial damage in VKC.[1]

Macrophages

Besides exotoxin, monocyte chemotactic protein (MCP)-1, MCP-3, and RANTES, are highly expressed in limbal VKC tissues, primarily by macrophages.[1]

Other inflammatory mediators

Severity of VKC inflammation is due to proinflammatory cytokines like IL-1, IL-6, and IL-8. Other inflammatory cells like neutrophils, basophils, and macrophages releasing several potent proinflammatory mediators, enzymes, cytokines and leukotrienes are recruited in VKC. The presence of the characteristic symptoms observed in VKC, such as mucous secretion, conjunctival hyperemia, and chemosis are due to the action of leukotrienes which cause vessel vasodilation, edema, and hyperemia.[2]

Ocular surface damage through tear film instability is due to a down regulation of the major ocular surface trans membrane mucin, MUC5AC, (secretory mucous membranes which remove allergens and pathogens from the ocular surface and plays an important lubricating

activity in epithelial cells with up regulation of MUC 1, MUC 2, MUC 4, and MUC 16 mRNA expression.[5]

Furthermore, structural cells, such as epithelial cells, fibroblasts, and vascular endothelial cells, are stimulated by several mediators to produce other cytokines and proinflammatory factors, turning them into active cells in the inflammatory process. There is also an increase in Growth factors, such as FGF, PDGF, NGF, and TGF-b, EGFR, VEGF and several integrins. [1,3]
The consequence of the chronic production of all these factors is the resultant tissue remodeling reactions like epithelial changes, connective tissue deposition, edema, inflammatory cell infiltration, and glandular hypertrophy

Hormonal and neuroendocrine factors

Hormones and neuroendocrine factors may also influence the immune deviation and the response to environmental factors. The prevalence of VKC in males more than females and the spontaneous resolution of the disease at puberty show that sex hormones may play a relevant role in the pathophysiology of allergic diseases by reciprocal interactions between the immune and the endocrine system. Estrogen and progesterone receptors were overexpressed on the conjunctiva by eosinophils and other inflammatory cells. These hormones may bind to conjunctival receptors and exert a proinflammatory effect through the recruitment of eosinophils to the conjunctival tissue.[2,6]

This is the reason for the presence of sex-hormone related diseases such as gynecomastia, polycystic ovary syndrome, mammary broadenoma, and adiposogenital dystrophy in a few of these patients.[7] Amongst the neural factors, substance P, a neuropeptide present in corneal nerve fibres and high levels of nerve growth factor released by epithelial cells attributed to the corneal neuropathy in these patients.[8]
Although allergic diseases (Th2 disorders) and autoimmune diseases (Th1-mediated) are usually considered to be diametrically opposed in the immune response, VKC patients and their families were observed to have high prevalence of autoimmune diseases like Grave's disease, psoriasis, multiple sclerosis, diabetes mellitus, celiac disease, alopecia, rheumatoid arthritis, etc. probably due to Th2 suppression of Th1 immune response resulting in an imbalance.[9]

DIAGNOSIS

The diagnosis of VKC is mainly clinical through typical history, signs, and symptoms.
Skin prick test to identify the specific allergens and assessment of normal or high levels of serum-total IgE helps in the diagnosis. Blood cell count may also show an increased number of eosinophils, indicating that the disease is systemic.

Measurement of ECP in serum is useful to assess systemic eosinophil activation and is helpful for the patient follow-up. To diagnose VKC by local tests, cytology can be performed either by tear cytology or by conjunctival scraping. Eosinophils are regularly found in the active phase and the absence of eosinophils can indicate a nonactive phase of the disease, the result of anti-inflammatory treatment, or a misdiagnosis. Lymphocytes, macrophages, and neutrophils are present at variable percentages. Though basophils and mast cells may be found, their presence is not necessary for diagnosis. Measurement of specific IgE in tear fluid, though not specific, has been useful in VKC, reflecting a predominantly local production and an exclusively conjunctival hypersensitivity. VKC should be differentiated between chronic allergic conjunctivitis, phlyctenular keratoconjunctivitis, and trachoma as it is not always possible to fit these patients into one or the other category.[1]

MANAGEMENT

Since VKC is clearly not simply an allergic eye disease but with complex inflammatory mechanisms that are shared by other serious and chronic immunological disorders, measures aimed at stabilization of mast cells or histamine receptor antagonists alone is frequently insufficient for controlling conjunctival inflammation and the frequent corneal involvement. Close collaboration between ophthalmologists, allergists and paediatricians is recommended. The currently available topical drugs are effective in treating acute phases of VKC but Because of the chronicity and severity of the disease, avoidance of triggers and life-style planning must be accompanied by pharmacological treatments: topical ocular and non-ocular pharmacologic treatment, systemic pharmacologic treatments and immunotherapy.[10,11]

Non-pharmacologic management

Patients and parents should be counselled regarding the nature and duration of the disease, clinical characteristics and possible complications. Psychological support may be necessary in severe cases. The first line of VKC management is the identification of allergens and avoidance of those environmental factors that may exacerbate the disease.

Avoiding exposure to nonspecific triggering factors, such as sun, wind, and salt water, with the use of sunglasses, hats with visors, and swimming goggles should be recommended. Frequent hand, face, and ear washing should also be suggested. Application of cold compresses and preservative-free artificial tears help to provide symptomatic relief. Eye drops containing herbal extracts, such as chamomile-containing preparations, should be avoided because they may cross-react with sensitizing allergens.

Topical ocular pharmacologic treatment

Currently available topical drugs for allergic conjunctivitis belong to: vasoconstrictors, antihistamines, mast cell stabilizers, 'dual-acting' agents (with antihistaminic and mast cell stabilizing properties), non-steroidal anti-inflammatory agents, corticosteroids and immunosuppressive drugs.

Mast cell stabilizers

Mast cell stabilizers like 2% and 4% sodium cromoglycate (DSCG, cromolyn), nedocromil sodium 2%, lodoxamide tromethamine 0.1%, spaglumic acid 4% and N-acetyl aspartyl glutamic acid (NAAGA6%) are the first-line drugs for VKC. The dosing schedule is 4-6 times daily, and their onset of action is as late as 2 weeks. DSCG alone has limited effects in the treatment of VKC and is less well tolerated than newer anti-allergic compounds. Lodoxamide was shown to be superior to nedocromil, DSCG and NAAGA and it acts on multiple cells involved in allergic inflammation, neutrophils, monocytes, and platelets.

Antihistamines

Antihistamines act via histamine receptor (HR) antagonism to block the inflammatory effects of endogenous histamine and prevent or relieve the associated signs and symptoms. Most antihistamines used in the treatment of allergy are H1 receptor antagonists. While the first-generation antihistamines pheniramine and antazoline have a short duration of action, the newer antihistamines like levocabastine hydrochloride 0.05% and emedastine difumarate 0.05% have a longer duration of action (4-6 h), and are better tolerated. They are instilled four times daily for 3 months. In direct comparison with levocabastine, emedastine proved to be more effective in alleviating the signs of seasonal allergic conjunctivitis. A meta-analysis of randomized clinical trials in VKC evaluated the efficacy of common anti-allergic eye drops (levocabastine, lodoxamide, mipragoside, NAAGA, nedocromil sodium, DCG) and among these, lodoxamide appeared to be the most effective.

Topical antihistamines with multiple anti-inflammatory activities

New antihistamines that combine mast cell stabilizing properties and histamine receptor antagonism, such as alcaftadine, azelastine, bepotastine, epinastine, ketotifen, and olopatadine, are advantageous in that the symptomatic relief given by immediate histamine receptor antagonism alleviates itching and redness, coupled with the long-term disease-modifying benefit of mast cell stabilization. All of these medications are well tolerated and none are associated with significant ocular drying effects. Topical decongestants can be used in mild and moderate forms of VKC. However, they do not reduce the allergic response because they do not antagonize any of the mediators of allergic inflammation. Also, their prolonged use can lead to rebound hyperemia and conjunctivitis medicamentosa.

Non-steroidal anti-inflammatory drugs

Topical NSAIDS like indomethacin 1%, ketorolac 0.5%, and diclofenac 0.1% inhibit both cyclooxygenase (COX)-1 and COX-2 enzymes and have a proven effect on itching, intercellular adhesion molecule-1 expression, and tear tryptase levels.

Topical corticosteroids

Moderate to severe VKC with persistent severe symptoms, thick mucus discharge with moderate to severe corneal involvement, numerous and inflamed limbal infiltrates and/or giant papillae, are the indications for corticosteroids, though they should be avoided as the first line of treatment in VKC. If steroids are used, low potent ones like fluorometholone, loteprednol, difluprednate and rimexolone should be used first. Dosages are prescribed in pulses of 3 to 5 days according to the severity.

Calcineurin inhibitors and other immunomodulators

Cyclosporine A (CsA) in VKC acts by blocking Th2 lymphocyte proliferation and interleukin-2 production. It inhibits histamine release from mast cells and basophils through a reduction in IL-5 production, and may reduce eosinophil recruitment and effects on the conjunctiva and cornea. CsA 1% or 2% emulsion in castor or olive oil instilled four times daily can serve as a good steroid sparing alternative. Tacrolimus eye ointment 0.03% and 0.1% was also effective and safe in the treatment of VKC.

Systemic pharmacologic treatment

Systemic treatment with oral antihistamines or antileukotrienes can reduce the severity of flare-ups and generalized hyper-reactivity. These drugs which include acrivastine, cetirizine, beastie, fexofenadine, loratadine, desloratadine and levocetirizine have sedating and drying effects. Omalizumab, an anti-IgE recombinant, humanized, non-anaphylactogenic antibody, directed against the receptor-binding domain of IgE, may be used in VKC patients with high levels of total serum IgE.

Specific immunotherapy

Allergen-specific immunotherapy (SIT) is indicated only when a clearly defined systemic hypersensitivity to identified allergens exists and it was more effective than topical treatment in improving clinical symptoms and reducing total serum IgE.

Surgical treatment

Supratarsal injection of either a short-or intermediate-acting corticosteroid is used for treating refractory VKC. Surgical removal of corneal plaques is recommended to

alleviate severe symptoms and to allow for corneal re-epithelization. Giant papillae excision with intraoperative 0.02% mitomycin-C±cryotherapy±amniotic membrane transplantation (AMT) followed by CsA topical treatment may be indicated in cases of giant papillae. AMT following keratectomy can be used for treatment of deep ulcers.

NOVEL APPROACH TOWARDS VKC

Recent studies identified a novel proallergic molecule, thymic stromal lymphopoietin (TSLP), a kind of interleukin 7-like cytokine, which supported the Th 2 type immune response in VKC. This molecule was shown to activate dendritic cells through interaction with TSLP receptor (TSLPR) expressed by dendritic cells and then these cells would express OX40 ligands (OX40L) that interact with OX40 to prime CD4+ T cells to produce proallergic cytokines IL-4, IL-13, and IL-5 to induce an inflammatory Th2 type response and initiate allergic inflammation.[12]

Lacrytest (ADIATEC S.A, Nantes, France) is a rapid immunoassay for total IgE determination in tears which indicates, in a qualitative manner, the presence of total class E immunoglobulin in tears with levels above the normal value (<2 KU/l, 3 ng/ml).This test could be helpful to ophthalmologists to confirm an IgE-mediated reaction or VKC if the result is positive.[13] Recently, the mucous component of the tear film was evaluated by tear ferning test (TFT) and it could be used as a simple, inexpensive, and low-invasive test to clinically evaluate the tear film. It could also be a marker of therapeutic efficacy in patients with VKC.[5] The efficacy of honey drop which has antibacterial and anti-fungal properties in treating VKC was also noted which helped in reducing allergic symptoms, reducing limbal papillae and hyperemia[14,15]

CONCLUSION

Multitude of cells like histamine, chemokines, macrophages, eosinophils, structural proteins as well as hormonal and neuroendocrine factors play role in the inflammatory process of the disease, so treatment options should be considered in a step ladder approach keeping in mind the wide variety of cellular and environmental factors.

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