

The Pathophysiology of Ocular Allergy: Current Thinking

C Stephen Foster, MD, FACS, Professor of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA.

Summary

Seasonal allergic conjunctivitis is the only ocular disease to involve solely Type-1 hypersensitivity, the other main forms of ocular allergy – perennial allergic conjunctivitis, vernal and atopic keratoconjunctivitis and giant papillary conjunctivitis – each having a more complex immunological basis and a chronic inflammatory component. Involvement of secondary inflammatory cells, particularly eosinophils, in addition to the mast cells resident in the conjunctival substantia propria, can lead to more serious corneal damage with vision-threatening potential. Thoughtful management of allergic conjunctivitis is needed in order to control the ocular inflammation without incurring steroid-induced side-effects, and patient education is also an important factor in maintaining optimal allergen avoidance, especially in the more severe and chronic cases. Laboratory models can be helpful in assessing the potential of new drugs, and SWR mice (topically sensitised and challenged with short ragweed) show clinical signs of allergic conjunctivitis, together with mast cell and eosinophil involvement, remarkably similar to the human pathophysiology. The antiinflammatory activity of both steroids and nedocromil sodium observed in this animal model supports therapeutic evidence of the usefulness of second-generation mast cell stabilising drugs in the treatment of ocular allergy.

Introduction

Ocular allergy is generally split into five broad categories: – seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis, giant papillary conjunctivitis and atopic keratoconjunctivitis. In only one of those disorders is the classic Gell and Coombs, Type-1, hypersensitivity reaction the *only* hypersensitivity reaction involved, and that is seasonal allergic conjunctivitis. In all of the other disorders at least Type-4, and possibly other types of

immuno-reactivities come into play as well, producing chronic inflammation.

It is primarily the connective tissue mast cell that is present in the substantia propria of the conjunctiva, which may be surprising or not to the clinical allergist but is fortunate for the patient, in that this cell type (unlike mucosal mast cells) is sensitive to most of the mast cell stabilising agents. However, there exists a panoply of chemoattractants and vasoactive substances, liberated not only by mast cells but also by eosinophils and other cells, that produce ocular pathology in patients with ocular allergic disorders. It is most unlikely, therefore, that one-to-one competitive inhibitors – whether of histamine receptors or leukotriene synthesis – will alone be sufficient treatment for patients with ocular allergy.

The essential area that many ophthalmologists neglect most frequently is in taking a thorough history and providing the kind of education to a patient that can allow him or her to participate in proper environmental control. All too many ophthalmologists inappropriately resort to generalised suppression of inflammation through the use of topical steroids, with potentially deleterious effects.

Ocular pathophysiology

Seasonal allergic conjunctivitis

The typical ocular picture of seasonal allergic conjunctivitis is often accompanied by nasal symptoms of allergic rhinitis and may also be marked by swelling of the eye lids and the appearance of 'allergic shiners'. Generally, however, the ocular manifestations are relatively obscure – that is, the patient does not have a bright red eye, and typically complains of itching far out of proportion to the signs that the doctor is actually able to observe.

This condition, although annoying and aggravating, like perennial allergic conjunctivitis is non-vision-threatening. A variety of therapies can be used including allergen avoidance, topical anti-histamines and topical mast cell stabilising agents. A study published two years ago by Blumenthal et al.¹, that demonstrated the effectiveness of nedocromil sodium ophthalmic solution in the care of patients with seasonal allergic conjunctivitis, was done correctly –

during 'decent' pollen count seasons – and showed a dramatic reduction in both signs and symptoms of patients on active ingredient compared to placebo.

Vernal keratoconjunctivitis

VKC is a disorder of profound visual importance. It is a recurrent conjunctivitis which is typically seasonal (hence the name 'vernal'), is clearly allergic, and which typically occurs in young males for reasons that are not clear. Extreme itching is the primary symptom. If the doctor imagines that the patient has vernal conjunctivitis and the patient is not spontaneously complaining of itch, the diagnosis is probably not correct. Burning eyes, blurred vision and 'foreign body' sensation are other symptoms, and the signs include conjunctival injection and profound ptosis or droop of the upper lid. A lardaceous, cream-coloured, ropy mucous secretion is also typical, but the classic hallmark of this disease is the presence of giant excrescences – the so-called 'cobblestone' papillae – on the upper tarsal conjunctivae (Fig.1). Limbal papillae may also occur at the corneoscleral limbus (this being more common in people of non-Caucasian origin) and these often have white excrescences on their apices. Examination of

a scraping treated with Wright's-stain will show these white areas, known as Horner-Trantas' dots, to be rich in eosinophils. However, it is the corneal problems that are associated with VKC that produce the vision loss – and vision loss is not rare in this condition. It is a pity that still today many ophthalmologists tell mothers of youngsters with this disease that it is a problem that she should not worry about: 'It is trivial, and junior will outgrow this problem by and by'. Whilst it is true that junior *will* probably outgrow this problem, in the process of doing so he may well end up blind from irreversible keratopathy. This begins with superficial punctate epitheliopathy, followed by a 'shield ulcer'. This is a stagnant or trophic, non-healing, persistent epithelial defect, which may then become secondarily infected through the imprudent use of topical steroids, resulting in a blinding corneal scar. Nedocromil sodium has also been shown to be unequivocally effective in the treatment of patients with VKC², as was sodium cromoglycate before it³.

The role of eosinophils in ocular allergy is vastly under-appreciated, at least by many ophthalmologists. The shield ulcer almost certainly occurs because of eosinophil major basic protein (MBP) and perhaps other vasoactive amines and substances

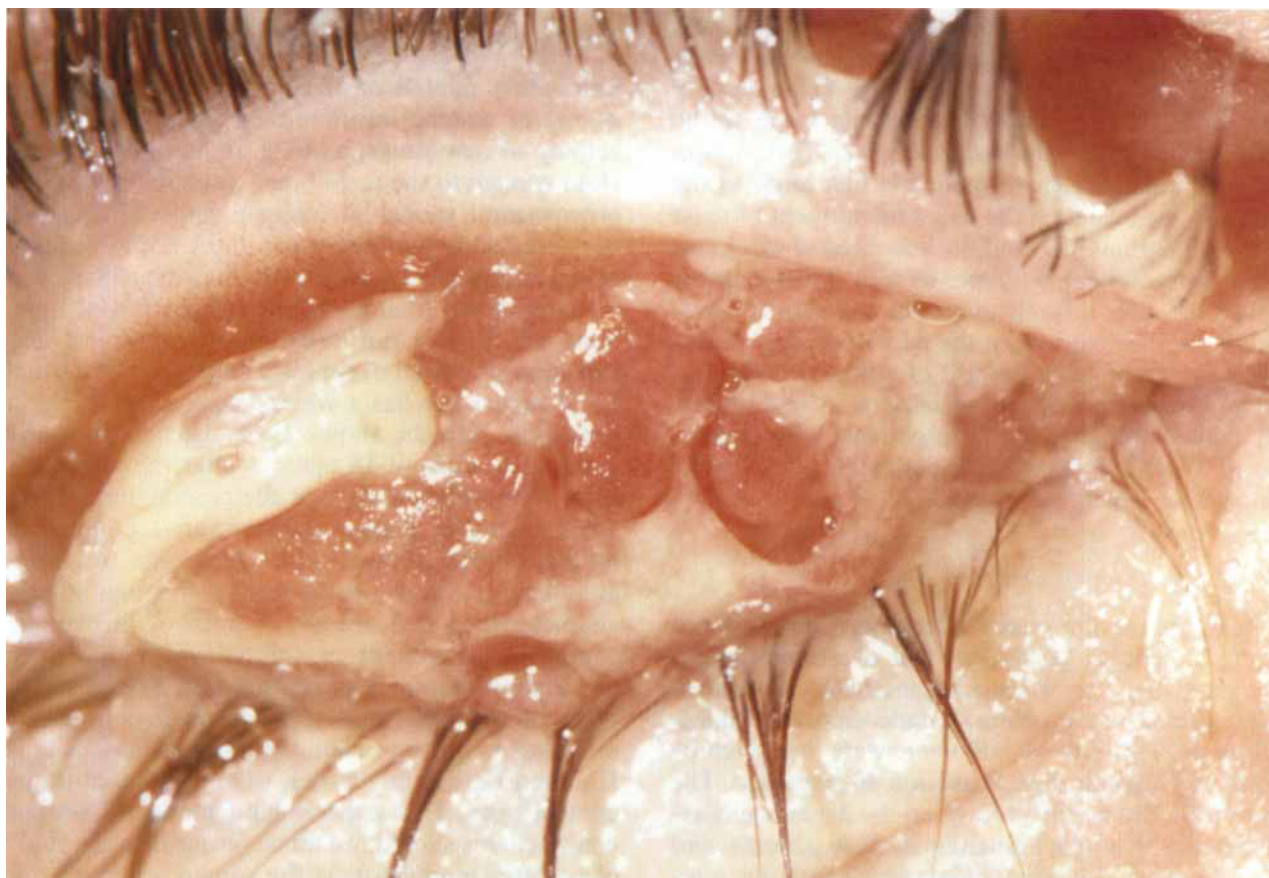


Fig. 1. Giant papillary conjunctivitis in a patient with vernal keratoconjunctivitis. Note the large 'cobblestone' excrescences in the upper tarsal conjunctiva.

present in the pre-ocular tear film, and not simply because of the histamine that is making the patient itch and scratch. Eosinophil MBP is extremely toxic to corneal epithelial cells; in addition, it is probably associated with the sustained mast cell degranulation that is typically seen in the more chronic forms of ocular allergy: – vernal and atopic keratoconjunctivitis.

Giant papillary conjunctivitis

Giant papillary conjunctivitis (GPC) is somewhat less of a problem as it is non-vision-threatening and is now to some extent on its way out because of improving contact lens materials and the use of disposable lenses. GPC develops as a result of the adherence of environmental allergens onto the surface of contact lenses (or ocular prostheses or sutures), leading to sensitisation of the tarsal conjunctiva due to the wiping of that tissue over the contaminated lens surface thousands of times each day. In the person who is predisposed to developing this problem, it progresses in terms of the number and size of the bumps on the upper tarsal conjunctiva. At first, also, the patient begins to develop some itch and decreased lens tolerance (stage 1) and, as the problem progresses further, some blurring of vision (stage 2). Excessive lens movement begins as the bumps become large enough to 'grab' at the lens with each blink (stage 3) and then finally (stage 4) the process looks exactly like mild VKC, sharing some of the same histopathologic characteristics. This occurs because sensitisation to materials that stick to the lens surface results in the usual recruitment of mast cells and eosinophils, and the liberation of cytokines which attract other cell types as well. The treatment of this disorder is firstly to modify the patient's routine behaviour, and often the lens itself, and if necessary to commence the use of adjunctive medical therapy such as mast cell stabilisers, as reported by Donshik ⁴ and Buckley ⁵, in patients with stage 1, 2 and 3 GPC. Stage 4 GPC patients must have the lens discontinued.

Atopic keratoconjunctivitis

Finally among the ocular allergies is the most potentially blinding condition: that of atopic keratoconjunctivitis, or keratoconjunctivitis associated with eczema: – a problem of under-appreciated significance. This linkage and name were first given by Michael Hogan in San Francisco 40 years ago. The symptoms are predictable, given the ocular signs associated with atopic dermatitis in these patients, and include chronic conjunctivitis which may be scarring, formation of papillae in the upper tarsus and, always, the development of keratopathy. Interest-

ingly, there are other ocular problems that are associated with this disease, including cataract, even in those patients who have never used topical steroids, and a rather substantial number of individuals with herpes keratitis and retinal detachment: the latter almost certainly because of trauma due to repeated eye-rubbing. Among a group of individuals with atopic keratoconjunctivitis from our Boston clinic, fully one-third were legally blind in one eye at the time of their first visit, and typically the corneal phenomena were the vision-limiting factors. Caring for individuals with atopic keratoconjunctivitis can be extraordinarily complex and usually requires an interdisciplinary approach to obtain success. Hospitalisation is often useful as a first step, to remove the patient from his (or her) environment and get him under control. Allergen avoidance measures (such as removal of pets) require a degree of patient co-operation which may involve some tough decisions affecting lifestyle and even relationships; however, as the eye condition deteriorates, the patient is left with little choice but to modify his own environment. Once this is under control, corneal grafting and subsequent treatment with systemic cyclosporin and topical mast cell stabilisers is often sufficient to prevent further problems.

Laboratory models of allergic conjunctivitis

Laboratory models of allergy can be an invaluable means of gaining information about the potential activity of new drugs, as long as these models are close enough to the real human situation. One such experimental model of allergic conjunctivitis has been created in our laboratory in the SWR strain of mouse, using short ragweed sensitisation achieved in the natural way, that is without using artificial injections and the like, but rather nasal and topical sensitisations followed by topical challenge. The normal SWR mouse eye has a white conjunctiva which, in sensitised animals, shows clear signs of chemosis and injection about 15 minutes after ragweed challenge. These clinical signs of allergic conjunctivitis in SWR mice after allergen challenge are accompanied by infiltrations of mast cells (often seen to be degranulating) and eosinophils: histopathologic characteristics that are also typical of the human condition. Treatment of this mouse model with nedocromil sodium is associated with a stabilisation of the mast cells, and a down-regulation of the manufacture of pro-inflammatory cytokines such as IL-6 and IL-4 in the tissues, when compared to the control eyes. This experimental model of allergic conjunctivitis should, we think, be useful in the study of potential modulators of the human ocular allergic response. It is quite clear from our studies to date that both steroids and nedocromil sodium have a

major effect on this laboratory model in comparison to control treatment with phosphate buffered saline, and in particular we have found a tremendous reduction in the number of eosinophils, and to a lesser extent the number of mast cells, seen in the tissue specimens.

Conclusions

In conclusion, it is important to emphasise that allergic eye disease is not the trivial problem envisaged by many allergists; it is epidemiologically important and of a blinding potential. It is clear, however, that long term steroid therapy is inappropriate, and that antihistamines affect only a small part of the panoply of chemoattractants and cytokines that are liberated. Mast cell stabilisers have revolutionised our care of patients with this problem, and it would appear that second-generation mast cell stabilisers such as nedocromil sodium are considerably more effective than the first-generation sodium cromoglycate.

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