

Atopic keratoconjunctivitis: present day diagnosis

Diyaa Rachdan, Deepa Rajeswari Anijeet, Sunil Shah

Atopic keratoconjunctivitis (AKC) is a rare but serious chronic allergic eye disease. It can involve the cornea, conjunctiva and the eyelids and ranges in severity from a mild condition to a disease causing blindness.¹ Guglielmetti² defined AKC as:

A chronic ocular surface non-infectious inflammatory condition with the following clinical characteristics: (1) Always associated with other atopic conditions, (2) Occurring at any time point in the course of the associated atopic disease, and independent of its degree of severity, (3) Evidence of corneal involvement at some time in the course of the disease.

AKC affects both children and adults,^{1 3 4} typically presenting in the late teens and early 20s.²

The disease is bilateral, and patients present with photophobia, blurry vision, itching, burning sensation, red eyes and mucoid discharge.⁵

Clinically, the eyelids may have severe atopic dermatitis with eczema that can be chronic or relapsing. Staphylococcal blepharitis is also a common finding.³ Conjunctivae are normally chemosed with limbal hyperaemia and small to medium-size papillary reaction of upper and lower palpebral conjunctivae. In severe cases, sub-epithelial conjunctival fibrosis may result in scarring, cicatrisation, fornical shortening and even symblepharon formation.⁶ The corneal involvement can be mild with punctuate epithelial erosions or severe with shield ulcers leading to scarring and peripheral vascularisation.² Bacterial, viral or acanthamoeba keratitis are also sometimes encountered.

The immunopathogenesis of AKC is not fully understood, but involves the release of different cytokines by effector cells² (mast cells, eosinophils, T cells and conjunctival epithelial cells).^{7 8} Following activation, the effector cells release mediators that predominantly activate T helper

cells-1 (Th1).⁹ Eosinophils, which are pathognomonic of AKC, release a variety of cytokines that modify other white cell activities as well as its own activity including: interleukin-4 (IL-4) which stimulates B cells and IL-8 which is a potent neutrophil chemoattractant,² eosinophil cationic protein (ECP),¹⁰ eotaxin-1 and eotaxin-2.¹¹

As a result, cytokines are released from Th1 and T helper cells-2 (Th2) including IL-2, interferon-gamma and IL-12,² IL-8⁷ and IL-33,¹² which facilitate a delayed hypersensitivity reaction and a severe inflammatory response.

Among the chronic allergic eye diseases, AKC is the most debilitating because of its chronicity and the potential loss of vision secondary to frequent corneal complications.^{1 2 4}

Due to the overlap between the different types of chronic allergic disease, diagnosing AKC can be challenging. In the majority of cases, the diagnosis can confidently be made based on the history together with the characteristic clinical features of AKC.

The need for a definitive tool for the diagnosis of AKC arises in atypical clinical situations or where severe inflammation may necessitate the use of systemic immunosuppression.²

Serum IgE and skin prick tests are non-specific allergic tests. Inada has described immunochromatography of tears to detect both allergen specific IgE and total IgE in patients with allergic conjunctivitis disease including AKC; the levels of IgE in tears using this method correlated with the clinical severity of the allergic conjunctivitis disease.¹³

On the other hand, conjunctival histopathology in AKC only showed a reduction in the number of eosinophils, which are less degranulated compared to those in vernal keratoconjunctivitis.¹⁴

Recently, confocal scanning laser microscopy has been described as an effective, non-invasive tool for the quantitative evaluation of the ocular surface in patients with AKC.⁶ Another study found that there is a strong positive correlation between the inflammation status evaluated by brush cytology and the severity of

conjunctival inflammation evaluated by *in vivo* confocal microscopy.¹⁵

Levels of ECP in patients with AKC were previously found to be increased and considered to be a reflection of eosinophil activation.¹⁶

More recently, in a study by Wakamatsu *et al* on the anti-inflammatory effects of tacrolimus eye drops and their efficacy in controlling clinical signs in AKC patients, changes in ECP levels in the tears of patients with AKC were measured and clinical signs monitored. Tear ECP levels after treatment with topical tacrolimus were significantly reduced compared to the pre-treatment level, with strong positive linear correlations between ECP values and clinical signs.⁵

In the April issue of the journal, the same authors found high levels of ECP in the tears of patients with corneal epithelium damage in comparison with a control group. They then demonstrated that ECP levels in tears were useful markers for determining the severity of ocular surface disease in AKC, while tear IgE had no correlation with clinical signs even though higher total IgE levels were detected in AKC tears when compared with the control group.¹⁷

The importance of these finding is that even though ECP levels were found to be high in the serum of patients with AKC, they were a marker for systemic eosinophil activation rather than a specific indication for the ocular severity of the condition and hence demonstrate the important advantage of measuring ECP in tears rather than in serum.

Accordingly, the ECP levels in the tear film of patients with AKC can serve as an additional objective test with high accuracy for monitoring eosinophilic activation, and hence the severity of the condition at the time of the test.

Finally, even with all the currently available tests, it is still not possible to make a firm laboratory diagnosis of AKC, as all the tests proposed so far can only confirm a diagnosis of allergic eye disease but not determine the subtype. More research is still needed to address the issues that necessitate the need for a definitive tool to confirm a diagnosis of AKC. Consequently, the new finding of tear ECP levels and their value can be utilised in clinical trials to assess the inhibitory properties of disease modulating agents and correlation of these biochemical effects with clinical signs and symptoms.

Contributors All three authors have contributed significantly to the content of the editorial.

Birmingham and Midland Eye Centre, City Hospital, Birmingham, UK

Correspondence to Professor Sunil Shah, Birmingham and Midland Eye Centre, City Hospital, Dudley Road, Birmingham B18 7QH, UK; sunilshah@doctors.net.uk

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REFERENCES

1. **Foster CS**, Calonge M. Atopic keratoconjunctivitis. *Ophthalmology* 1990;**97**:992–100.
2. **Guglielmetti S**, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2010;**10**:478–85.
3. **Tuft SJ**, Kemeny DM, Dart JK, *et al.* Clinical features of atopic keratoconjunctivitis. *Ophthalmology* 1991;**98**:150–8.
4. **Power WJ**, Tugal-Tutkun I, Foster CS. Long-term follow-up of patients with atopic keratoconjunctivitis. *Ophthalmology* 1998;**105**:637–42.
5. **Wakamatsu TH**, Tanaka M, Satake Y, *et al.* Eosinophilic cationic protein as a marker for assessing the efficacy of tacrolimus ophthalmic solution in the treatment of atopic keratoconjunctivitis. *Mol Vis* 2011;**17**:932–8.
6. **Hu Y**, Adan ES, Matsumoto Y, *et al.* Conjunctival in vivo confocal scanning laser microscopy in patients with atopic keratoconjunctivitis. *Mol Vis* 2007;**13**:1379–89.
7. **Enriquez-de-Salamanca A**, Calder V, Gao J, *et al.* Cytokine responses by conjunctival epithelial cells: an in vitro model of ocular inflammation. *Cytokine* 2008;**44**:160–7.
8. **Matsuda A**, Ebihara N, Yokoi N, *et al.* Functional role of thymic stromal lymphopoietin in chronic allergic keratoconjunctivitis. *Invest Ophthalmol Vis Sci* 2010;**51**:151–5.
9. **Metz DP**, Hingorani M, Calder VL, *et al.* T-cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* 1997;**100**:817–24.
10. **Montan PG**, van Hage-Hamsten M. Eosinophil cationic protein in tears in allergic conjunctivitis. *Br J Ophthalmol* 1996;**80**:556–60.
11. **Leonardi A**, Jose PJ, Zhan H, *et al.* Tear and mucus eotaxin-1 and eotaxin-2 in allergic keratoconjunctivitis. *Ophthalmology* 2003;**110**:487–92.
12. **Matsuda A**, Okayama Y, Terai N, *et al.* The role of interleukin-33 in chronic allergic conjunctivitis. *Invest Ophthalmol Vis Sci* 2009;**50**:4646–52.
13. **Inada N**, Shoji J, Kato H, *et al.* Clinical evaluation of total IgE in tears of patients with allergic conjunctivitis disease using a Novel Application of the immunochromatography method. *Allergol Int* 2009;**58**:585–9.
14. **Rich LF**, Hanifin JM. Ocular complications of atopic dermatitis and other eczemas. *Int Ophthalmol Clin* 1985;**25**:61–76.
15. **Wakamatsu TH**, Okada N, Kojima T, *et al.* Evaluation of conjunctival inflammatory status by confocal scanning laser microscopy and conjunctival brush cytology in patients with atopic keratoconjunctivitis (AKC). *Mol Vis* 2009;**15**:1611–19.
16. **Leonardi A**, Borghesan F, Faggian D, *et al.* Eosinophil cationic protein in tears of normal subjects and patients affected by vernal keratoconjunctivitis. *Allergy* 1995;**50**:610–13.
17. **Wakamatsu TH**, Satake Y, Igarashi A, *et al.* IgE and eosinophil cationic protein (ECP) as markers of severity in the diagnosis of atopic keratoconjunctivitis. *Br J Ophthalmol* 2012;**96**:581–6.



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