

Atopic Keratoconjunctivitis

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A 31 year old male patient presented to us, referred from an ophthalmologist in New York, with a diagnosis of 'recent corneal tear in the right eye'. The patient complained of persistent 'soreness', excessive tearing, and photophobia. He had had these complaints intermittently, along with yellowish mucous discharge (especially upon awakening) for many years and many eye drops and oral medications had been prescribed by many ophthalmologists and dermatologists over the years. This particular episode was severe and unremitting, and hence the referral.

The patient's past medical history was significant for atopic dermatitis (AD or eczema) and exercise-induced asthma. The family history was significant for myocardial infarction in his father, and cancer, specifically colorectal cancer, and the patient's mother had ovarian cancer. The patient was a non-smoker, was a student working part time as a waiter, and occasionally drank alcohol. At presentation, his medications included systemic prednisone (60 mg daily), topically applied (skin) tacrolimus cream and triamcinolone. He was also using Lotemax, Alrex and Vigamox eye drops in the right eye four times daily, Restasis in the left eye twice daily, and Celluvisc in both eyes as needed. He was allergic to Dovonex cream, and had a history of intolerance to systemic cyclosporine (hypertension and nephropathy).

General physical examination disclosed eczema of the face and chest. Visual acuities were 20/200 OD and hand motion OS, intraocular pressures were 12 and 15, and slit lamp biomicroscopy showed 3+ conjunctival injection in the right eye, with ciliary flushing, and a corneal epithelial defect with stromal opacification, glue, and bilateral keratoconus.

Serologic tests ordered included CBC (WBC 13.6, eosinophil count 47/mm³, normal range 50-300, serum IgE (2650 IU/ml; upper limit of normal 248). At this point an assessment of acute corneal hydrops, keratoconus, and atopic keratoconjunctivitis (AKC) was made, and it was determined that the best course of therapy would be to treat the patient with intravenous Zenapax, 75 mg/infusion (determined by his weight), systemic tacrolimus 4 mg/day (as he had already been on multiple cycles of high-dose systemic corticosteroid therapy) and a scleral lens for protection of the epithelial defect and acute hydrops.

After a course of five monthly Zenapax infusions, the patient was dramatically improved both from the ocular surface and the dermatological standpoint, with almost all of his skin lesions resolving. The patient's visual acuity returned to 20/60 and 20/20, and the injection, flush and corneal hydrops also resolved completely.

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AKC, a potentially blinding condition, is also responsible for causing much ocular morbidity in patients from a peculiar set of other ocular conditions. Its chronic, unremitting (without treatment) course has much to do with its eventual blinding potential, as opposed to the other self limited conjunctivitis such as vernal keratoconjunctivitis, seasonal allergic conjunctivitis, or giant papillary conjunctivitis. As the name implies, it is an atopic (allergic) condition (derived from the Greek 'atopos' for aberrant or out of place) occurring in patients in association with atopic dermatitis or eczema. Recent evidence suggests that AKC and eczema are not only caused by the classic Type I hypersensitivity (from Gell & Coomb's original classification system) but also by a Type IV (delayed-type) hypersensitivity. This is supported by the clinical findings that some patients have neither peripheral eosinophilia nor high IgE levels (seen in classic Type I hypersensitivities), have negative RAST tests (radio-immuno-allergosorption testing that measures IgE levels for specific common allergens – performed to try and identify the patient's particular sensitivities) and that this particular subset of patients do not respond favorably to treatment with antihistamines. These patients' symptoms are triggered by nonspecific stimuli, such as cold wind, dust, or even sunlight, and they show a general, non-specific 'across-the-board' type hypersensitivity.

About 15-65% of patients with eczema have ocular involvement of AKC (different figures quoted by different authors) which may be unilateral or bilateral at presentation. Almost all patients eventually develop bilateral involvement, though it often starts off unilateral and asymmetrical. The symptoms of AKC are itching, burning, pain, redness, foreign body sensation, light sensitivity and blurry vision. Patients also complain of a stringy, ropy, mucoid discharge on awakening. Signs are typically more prominent in the lower conjunctiva, as opposed to vernal keratoconjunctivitis where they are seen in the upper conjunctiva. These include a pale, edematous, boggy and featureless conjunctiva (Figure 1) in the early stages, progressing to papillary hypertrophy, (Figures 2 and 3) subepithelial fibrosis, fornix foreshortening, and a progressive chronic cicatrizing conjunctivitis. Late complications include the development of trichiasis, entropion, madurosis and the resulting corneal sequelae. Keratopathy is the main cause of visual impairment in patients with AKC, starting with punctate epithelial erosions (they stain with fluorescein and not rose Bengal), persistent epithelial defects and eventually corneal neovascularization.

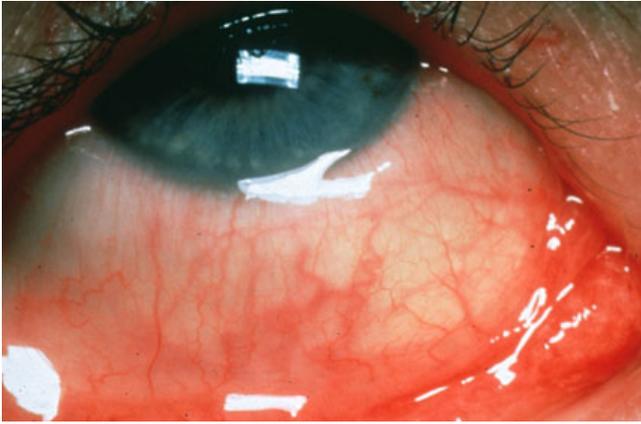
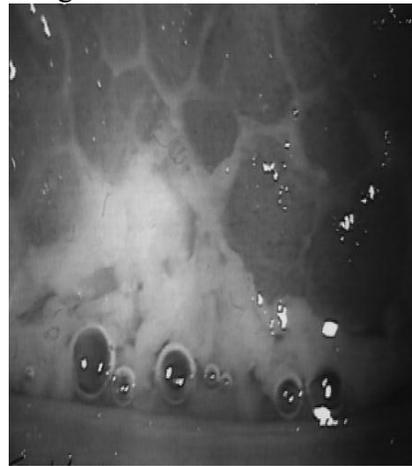


Figure 1



Figures 2 and 3

Other associated causes of ocular morbidity in patients with AKC are a high incidence of cataracts (mostly anterior or posterior subcapsular), a higher than normal rate of retinal detachment (both spontaneous or post-cataract or corneal transplantation), keratoconus, and herpes. Eczema herpeticum and herpetic keratitis occur in 14-17% of patients.

In histopathological specimens, increased numbers of mast cells and eosinophils are seen infiltrating the conjunctival epithelium and the substantia propria. Squamous metaplasia and increased numbers of fibroblasts and collagen deposition are also seen. Eosinophils are directly responsible for the corneal complications, as their toxic granule contents (eosinophil major basic protein, eosinophil derived neurotoxin, eosinophil lymphotoxin, and eosinophil protein X) have been detected in the beds of stromal ulcers and epithelial defects. The tears of patients with AKC contain high levels of IL-4 and 5, RANTES, ECP that selectively recruit, stimulate and encourage terminal differentiation of eosinophils. High numbers of IgE, B cells, T helper cells, IL 2 and the IL2 receptor have also been described in tears and in sera.

The treatment of AKC should include involvement of an allergist for identification of the provoking allergen(s) and education about avoidance of triggers. The triggering antigen may be identified in patients with skin patch testing against a panel of commonly occurring antigens, or in a more sophisticated manner by RAST testing.

Topical treatment with antibiotics for the associated staphylococcal blepharitis may be needed, and patients may also benefit from topical mupirocin treatment for their skin and eyelid eczema. Lubrication with artificial tears may be helpful, alongwith a dual acting antihistamine/mast cell stabilizer such as olopatidine or azelastine or epinastine. Topical corticosteroids may be periodically needed for flare-ups, but their use should be closely monitored and the prescriptions should be non-refillable, as their long term use predisposes to the development of cataracts and glaucoma.

Supratarsal injections of corticosteroids may be used in cases where there is an extreme conjunctival papillary reaction participating in the formation of a shield ulcer. However, the ulcer tends to recur after the effect of the corticosteroid has worn off.

In the most severe cases, systemic treatment with signal transduction inhibitors such as cyclosporine or tacrolimus may be needed to control the systemic immune dysfunction that leads to the ocular and dermatological manifestations. Systemic antihistamines can also benefit patients and reduce the itching, especially if taken at night, also help the patient to sleep better. Hydroxyzine is especially useful in this role. Plamapheresis has shown short term benefit in the severest cases.

Kerato-conus

The root 'kerato' means cornea and so keratoconus quite literally means a cornea that resembles a cone, as the shape of the cornea is progressively distorted in this disorder. The cornea becomes thin, steep and protrudes anteriorly. The nature of the protrusion may be overall (oval or globus keratoconus) or localized in the centre (the so-called nipple cone). Figures 3 and 4



Figure 3 Globus and nipple cones Figure 4 Oval cones

This results in progressive myopia, astigmatism and the need for higher and higher myopic spectacle prescriptions as the cornea becomes more and more steep. There is also intolerance to contact lens wear, with the lens sometimes falling off and getting dislodged. It can be thought of conceptually as trying to balance a saucer (or a plate) on the sharp tip of a cone, or even more simply as trying to balance a piece of paper on the tip of a pencil.

Keratoconus usually starts in the teenage years, sometimes unilaterally (eventually becoming bilateral), progresses slowly over time and eventually stabilizes. It is prevalent in all ethnic groups though there is a higher prevalence in men. The most common etiology of keratoconus (by far) is idiopathic, though it is associated with other systemic (Down's syndrome, Turner's syndrome, Ehlers-Danlos syndrome, Marfan's syndrome, atopy, osteogenesis imperfecta, mitral valve prolapse) and ocular diseases (vernal keratoconjunctivitis, blue sclerae, aniridia, ectopia lentis, retinitis pigmentosa, Leber's congenital amaurosis, hard contact lens wear and vigorous eye rubbing) It is thought that keratoconus is seen with a higher frequency in Down's syndrome and Leber's amaurosis because of blepharitis and the associated eye rubbing behaviours seen in these conditions. It is interesting to note that the bilaterality of keratoconus, its clustering in certain families, and results from twin studies do show some genetic basis for it. Many candidate genes have been identified, including those on chromosomes 16q, 20q and 20p, 21 (Down's), 17p (Leber's) There is also an association with HLA subtypes A26, B40, DR9,

The issue of contact lens wear and keratoconus is a perpetual chicken and egg story – which came first? Both hard and soft contact lenses do impose mechanical stresses on the cornea and cause thinning, so do they cause keratoconus? On the other hand, does keratoconus develop first, and when it is treated with hard contact lenses to try and alter the shape of the cornea, does it progress because of the additional stress?

On clinical examination, there are many signs that may be elicited in patients with keratoconus. Direct ophthalmoscopy yields the 'oil-droplet' reflex (Figure 5) and

retinoscopy the 'scissor reflex'. On downgaze, the convexity of the cornea 'indents' the lower lid margin resulting in Munson's sign, and the Rizutti sign refers to a sharp beam of light seen on the nasal aspect after temporal illumination.



Figure 5 – Oil droplet reflex seen in keratoconus

Slit lamp biomicroscopy discloses subtle Vogt's lines or striae, seen in the stroma of the cornea (Figures 6 and 7).



Figure 6

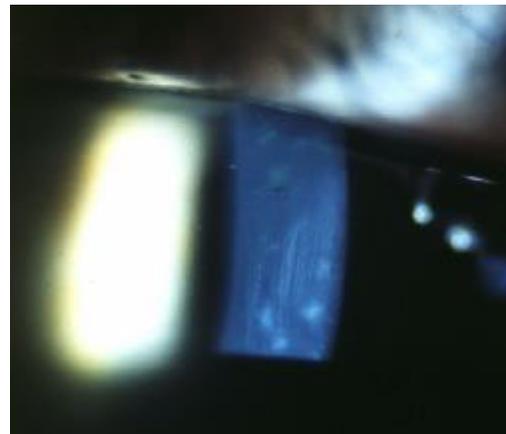


Figure 7

Enlarged corneal nerves, (Figure 8) epithelial iron deposits (Fleischer ring – Figure 9 – not to be confused with the Kaiser-Fleischer ring seen in Wilson's disease) and corneal thinning may also be seen in advanced cases.

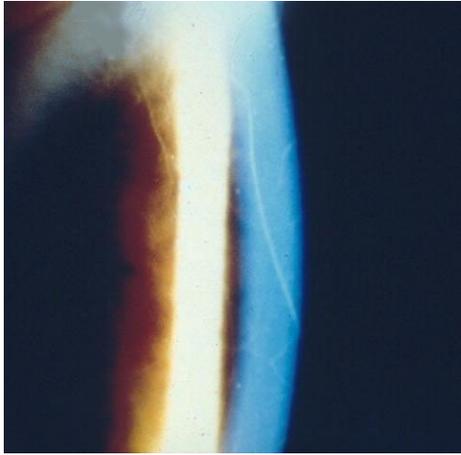


Figure 8 – Enlarged corneal nerves

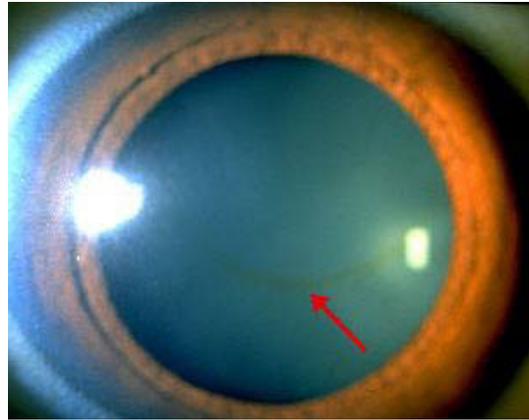


Figure 9

The diagnosis of keratoconus may be made by several modalities. The Placido disk (Figure 10) projects a series of concentric circles onto the cornea that are then analyzed for distortion or uneven distribution because of the uneven curvature of the cornea. Automated computer keratometry (with analysis of the mires – Figures 11 and 12), videokeratography, corneal pachymetry and histopathology may also be used. Videokeratography is a combined keratometer and photokeratoscope and is the best modality to document early findings and to monitor disease progression over time. On histopathology, the cornea is thin, with decreased numbers of collagen fibrils either as a result of defective formation or increased destruction (recent evidence points to both lines being active). A decreased activity of the protease inhibitors alpha 1 protease inhibitor and alpha 2 microglobulin has been documented, pointing to increased breakdown.

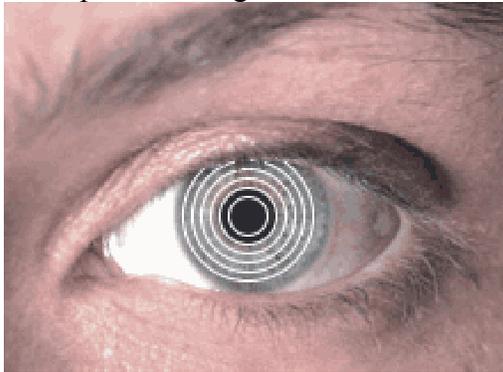


Figure 10 – Placido disk

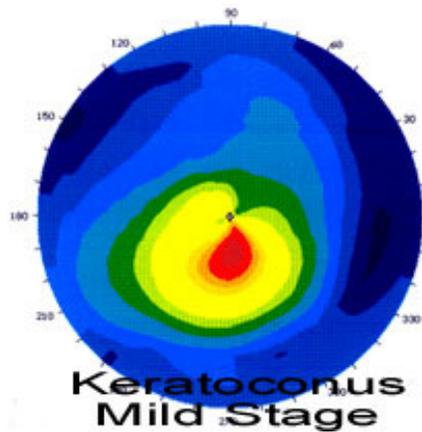


Figure 11

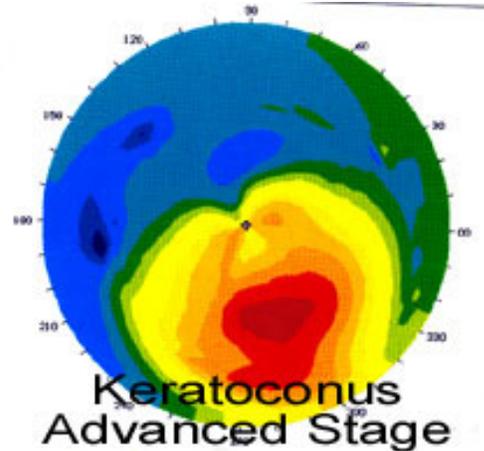


Figure 12

Every layer of the cornea may become involved in the pathology, with thin stroma and decreased numbers of collagen fibrils, defects in the architecture, breaks in Bowman's membrane, which later becomes filled with collagen and PAS + nodules, epithelial degeneration and downgrowth into the Bowman's membrane, and Descemet's membrane breaks – which leads to acute corneal hydrops.

Treatment of mild keratoconus in the early stages is by spectacle correction. In moderate cases, with irregular astigmatism, soft toric lenses may be used. Rigid gas permeable contact lenses are the mainstay of treatment in this stage. For patients intolerant to contact lenses and who have no scarring, epikeratoplasty or INTACS may be used. Complications can include abrasions, scarring, neovascularization from hypoxia, discomfort, and 'slippage' because of the irregular shape of cornea. Some practitioners now advocate penetrating keratoplasty instead of epikeratoplasty. Keratoplasty is also suited to those patients who have more advanced disease or associated scarring. It is important to note that keratoconus-associated thinning does not cause corneal perforation and that simple thinning is NOT an indication for keratoplasty. Complications are rare but can include graft rejection, postoperative astigmatism, a fixed dilated pupil (Urrets-Zavalía syndrome), or recurrence of KC. Even after keratoplasty about half of all patients still require some sort of contact lens wear due to myopia or astigmatism.

Corneal Hydrops

This is a rare complication seen in patients with long standing and advanced keratoconus when there is a break in Descemet's membrane.(Figure 13) This causes an acute influx of aqueous humor into the cornea, causing pain and a sudden decrease in vision. The classic description is a sudden onset, painful visual loss occurring at night or when the patient wakes up in the morning. The conjunctiva is injected and there is diffuse stromal opacity (a consequence of the aqueous influx – Figures 14 and 15). Healing usually occurs within 6-10 weeks, and may be accelerated by cycloplegics, corticosteroids, NSAIDs, hypertonic

saline, or patching with or without a soft bandage contact lens. Healing may occur with scarring (outside of the central visual axis – with minimal effects on visual acuity). Paradoxically, this causes contraction and flattening of the steep corneal curve, resulting in an increased tolerability to contact lenses.

Complications may include infection, (epithelial defects and stromal fluid and clefts facilitating the spread of microorganisms) pseudocyst formation, malignant glaucoma, and neovascularization or corneal rupture and perforation.



Figure 13

Figure 10 – Histopathology showing a ruptured Descemet's membrane and a cleft in the stromal layer

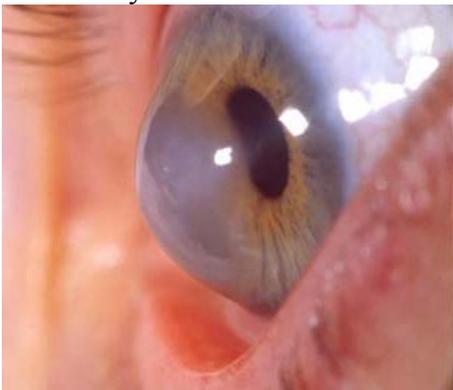


Figure 14

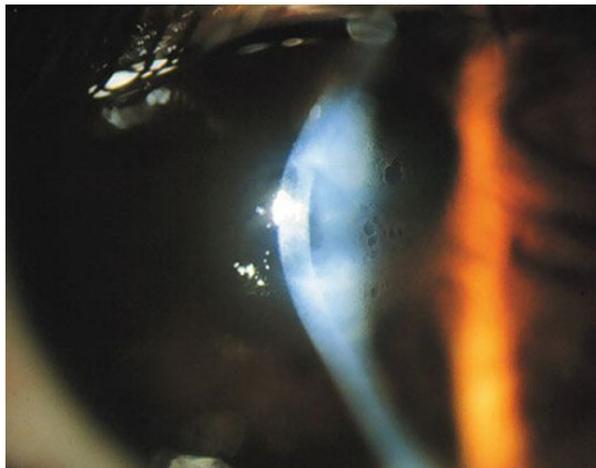


Figure 15

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Figures obtained from the Internet.