



Ocular Co-Morbidities of Atopic Dermatitis. Part I: Associated Ocular Diseases

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Abstract

Ocular diseases associated with atopic dermatitis (AD) may be sight-threatening. A general understanding of the pathophysiology, diagnosis, and treatment of atopic eye disease may assist dermatologists in knowing when to refer to ophthalmology and in co-managing these diseases with ophthalmologists. Ocular diseases associated with AD include eyelid dermatitis, keratoconjunctivitis, keratoconus, cataract, and retinal detachment. AD patients are also at higher risk for bacterial and viral ocular infections. The objective of this article is to provide a current review of ocular diseases that commonly affect AD patients. The pathogenesis, clinical manifestations, diagnosis, and treatment of ocular co-morbidities of AD will be discussed.

Key Points

Patients with atopic dermatitis (AD) may be at higher risk of several ocular complications, some of which are sight-threatening.

Ocular diseases associated with AD include eyelid dermatitis, keratoconjunctivitis, keratoconus, cataract, and retinal detachment, as well as bacterial and viral ocular infections.

Dermatologists may help prevent sight-threatening complications from these diseases by asking patients with AD about a history of ocular symptoms, and examining the periocular area.

1 Introduction

Atopic dermatitis (AD) affects approximately 17% of children and 5% of adults in the US [1, 2]. Although AD initially presents with cutaneous symptoms [3], AD patients have a disease severity-dependent risk of developing ocular symptoms during their lifetime [4]. Chronic rubbing and scratching of uncontrolled AD around the eyes may contribute to this risk. Even in the setting of well-controlled skin symptoms, ocular inflammation may be present and may warrant escalation of treatment [5]. The presence of ocular complications is indicative of severe and chronic AD, even in the absence of any visible skin symptoms [6]. Chronic, untreated ocular symptoms may permanently impair vision.

Despite the potential risk of vision loss, regular ophthalmological examination is not part of routine management for most AD patients [7]. Dermatologists should be aware of the potential ocular co-morbidities of AD in order to facilitate early diagnosis and appropriate treatment. This article identifies and reviews some of the most common ocular co-morbidities of AD. Eye complications associated with therapies used to treat AD are discussed in part 2 of this review [8].

2 Periocular Atopic Dermatitis

Overall, 20–42% of AD patients have eyelid and periocular skin involvement, which commonly presents with spongiotic changes and lichenification (Table 1) [9]. Dennie–Morgan folds (prominent creases below the lower eyelid margin or

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Table 1 Signs of atopic eye disease

Signs	Description
Skin findings	
Eczematous rash	
Lichenification	
Hyperpigmentation	
Hair findings	
de Hertoghe's sign	Loss of hair from the outer third of the eyebrow, often due to rubbing
Madarosis	Loss of eyelashes
Trichiasis	Misdirection of eyelashes towards the globe
Eyelid findings	
Dennie–Morgan folds	Prominent creases below the lower eyelid margin
Ptosis	Eyelid droop
Blepharitis	Inflammation of the eyelids
Eyelid hypertrophy	
Lagophthalmos	Failure to close the eyelids completely
Cicatrization	Scarring with distortion of the eyelid architecture
Ectropion	Eversion of the lid margin away from the globe
Entropion	Inversion of the lid margin towards the globe
Conjunctival findings	
Hyperemia	Redness, often due to vasodilation
Chemosis	Swelling or edema of the conjunctiva
Symblepharon	Adhesion of the palpebral conjunctiva to the bulbar conjunctiva

**Fig. 1** Chronic periocular atopic dermatitis resulting in eyelid hyperpigmentation and Dennie–Morgan lines

of the upper lid) are highly sensitive but not specific for AD, and are also considered a sign of respiratory atopy (Fig. 1) [10–13]. Orbital darkening is also associated with AD, but with less sensitivity [13]. Other AD-associated periocular findings may also occur in patients with eyelid dermatitis secondary to various other etiologies, including de Hertoghe's sign (loss of hair from the outer third of the eyebrow due to chronic rubbing) [14, 15], madarosis (a scarring or non-scarring loss of the eyelashes), ptosis (eyelid drooping), trichiasis (misdirection of eyelashes towards the globe), and lagophthalmos (failure to close the eyelids completely) due to chronic hypertrophy of the eyelids [16]. Lid malposition

with cicatricial entropion or ectropion (lower eyelid turning inwards or outwards due to scarring) may develop in severe cases.

3 Atopic Keratoconjunctivitis

Adults with AD have an increased risk of conjunctivitis (inflammatory disease of the ocular surface) or keratitis (corneal inflammation) [4]. Of the various etiologies for these conditions, atopic keratoconjunctivitis (AKC) is a particularly significant eye problem in AD patients. AKC was first defined by Hogan in 1952 as allergic conjunctivitis occurring with AD [17], and later by Guglielmetti et al. as a chronic, noninfectious, inflammatory condition affecting patients with a history of atopy and corneal involvement, independent of disease severity [16]. AD is present in 95% of AKC cases [16], and approximately 20–68% of patients with AD have AKC [9, 18]. AKC is more common in adults than children, and often presents between the second and fifth decades of life. There is an increased incidence with family history of atopy [9].

Pruritus is the hallmark symptom of AKC and patients often report tearing, mucoid discharge, and a foreign body sensation [19, 20]. The conjunctiva is often injected and chemotic due to dilated blood vessels and vascular leakage (Fig. 2) [17], and often there is associated blepharitis,

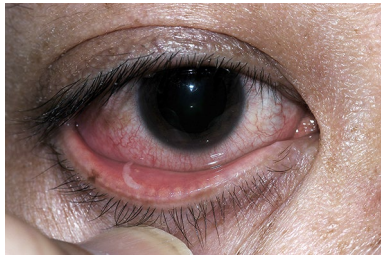


Fig. 2 Atopic conjunctivitis



Fig. 3 Atopic blepharoconjunctivitis with mucoid discharge (red and yellow colored diagnostic eye drops had been placed)



Fig. 4 Typical papillary conjunctivitis

sometimes called atopic blepharoconjunctivitis (Fig. 3) [19]. A papillary conjunctivitis of the upper and lower palpebral conjunctiva is a nearly universal finding in AKC (Figs. 4, 5). On eversion of the upper eyelid, papillae can be seen as a cobblestone arrangement of flattened nodules with central vascular cores. Chronic ocular surface inflammation may lead to larger, ‘giant’ papillae formation, subepithelial fibrosis, shortening of the fornix (the junction between the conjunctiva covering the eyelids and the conjunctiva covering the sclera), and symblepharon formation (adhesion of the palpebral conjunctiva to the bulbar conjunctiva of the globe) [21].

AKC is a clinical diagnosis based on a history of atopy and ophthalmic examination. The differential diagnosis includes other allergic eye diseases and etiologies of keratoconjunctivitis. Other forms of allergic eye disease include seasonal allergic conjunctivitis (SAC), perennial allergic

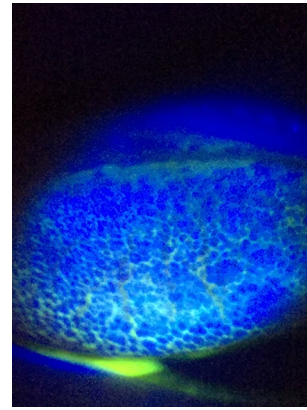


Fig. 5 Superior tarsal conjunctiva with fluorescein pooling around the papillae

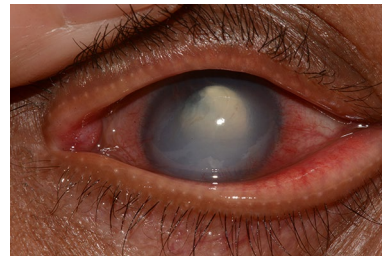


Fig. 6 Atopic keratoconjunctivitis, keratoconus, corneal scarring, and peripheral corneal neovascularization indicative of limbal stem cell failure

conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis in contact lens wearers. SAC is commonly due to pollen antigens and is closely associated with allergic rhinitis, while PAC symptoms often occur chronically and are most commonly due to dust mite antigens [22]. SAC and PAC are primarily mediated by immunoglobulin (Ig) E-mediated type 1 hypersensitivity and widespread mast cell activation [21], while VKC is a seasonally recurring, relatively rare ocular inflammatory disorder that may lead to corneal scarring and vision loss [23]. VKC typically presents in the pediatric population, particularly males in a warm climate [24]. Approximately one-half of VKC cases are associated with atopy, with asthma and allergic rhinitis being more common than AD in VKC cases.

Conjunctivitis itself does not typically present with pain, photophobia, or vision changes, but these symptoms may be present due to concurrent corneal complications [25]. In approximately 40% of cases, chronic atopic ocular surface inflammation leads to keratopathy (Fig. 6) [16]. Keratitis may progress from superficial punctate keratopathy seen only on slit lamp examination, to large corneal epithelial defects [26]. In the setting of chronic keratitis, the corneal epithelium may be unable to renew itself due to corneal

limbal stem cell failure. As a result, the patient may develop persistent epithelial defects, thinning, ulceration, perforation, secondary infection, corneal stromal opacification, and neovascularization. If suspected, based on patient-reported symptoms of eye pain, photophobia, or vision changes, urgent referral to a corneal specialist is warranted [26]. Without treatment, keratopathy may ultimately lead to significant morbidity and permanent vision loss.

Management of ocular and cutaneous pruritus is of paramount importance to manage AKC and prevent complications. Table 2 lists an overview of AKC treatments. In addition to optimizing skin treatment, safe, initial care by non-ophthalmologists may include use of non-vasoconstrictive artificial tears. Preservative-free preparations should be used if artificial tears are used more than four times daily. Due to the risk of ocular adverse effects, it is strongly recommended that corticosteroid eye drops are only prescribed by ophthalmologists, who may carefully monitor intraocular pressure (IOP). Corticosteroid eye drops should not be used by contact lens wearers. Adverse effects of corticosteroid eye drops include increased IOP, secondary glaucoma, irreversible optic nerve damage, cataract, and ocular infections [20]. The chronic, allergen-independent inflammation in AKC often requires the addition of topical or systemic immunosuppressive therapies, primarily with corticosteroids, calcineurin inhibitors, and interleukin (IL)-4R α inhibition [27, 28].

4 Keratoconus

AD is present in 18–41% of patients with keratoconus, a type of progressive corneal ectasia in which the normally spherical cornea thins and bulges into a cone-like shape, distorting the light that enters the eye before it reaches the retina [29]. AD patients have ten times the odds of developing keratoconus compared with the general population [4]. In AD, keratoconus may present at a younger age and may progress more rapidly [29].

Mechanical trauma from habitual eye rubbing is one proposed reason for the association between keratoconus and AD [30] as keratoconus occurs more frequently on the side of the dominant hand in atopic patients [31]. Collagen synthesis defects may also be important in the development of keratoconus. An inflammatory etiology for keratoconus in AD has also been suggested [32].

Symptoms of keratoconus include blurred vision, nearsightedness, and light sensitivity. On examination, the corneal bulge may be noted by having a patient look down and observing a positive ‘V’-shaped indentation of the lower lid (Munson’s sign) (Fig. 7). Definitive diagnosis requires referral to an ophthalmologist for slit lamp examination and corneal topography. Management may include rigid contact lenses, cornea collagen cross-linking, corrective lenses, or keratoplasty [33]. One potentially serious sequela of keratoconus is corneal perforation [34].

Table 2 Medical treatments for atopic keratoconjunctivitis

Therapy	Route of administration	Adverse effects
Early disease treatment		
Avoidance of allergens	NA	None
Cold compresses	Topical	None
Preservative-free artificial tears ^a	Ophthalmic drops	None
Antihistamines + mast cell stabilizers	Ophthalmic drops	Burning, stinging (rare)
Advanced disease treatment		
Corticosteroids	Ophthalmic drops, topical ointment, periocular injections	Increased intraocular pressure, cataract formation, glaucoma, secondary eye infections, ptosis, skin discoloration, skin atrophy, delayed wound healing
Calcineurin inhibitors	Ophthalmic drops, topical ointments	Irritation, stinging, secondary infections
Systemic medications		
Antihistamines	Oral	Drowsiness, dizziness, dry mouth, dry eyes
Prednisone	Oral	Hypertension, hyperglycemia, osteopenia
Cyclosporine	Oral	Hypertension, nephrotoxicity, hepatotoxicity
Tacrolimus	Oral	Nephrotoxicity, neurotoxicity, hyperglycemia
Dupilumab	Subcutaneous	Conjunctivitis, keratitis, injection site reactions
Allergen immunotherapy	Subcutaneous	Anaphylaxis

NA not applicable

^aIn contrast to formulations with preservatives, which may result in ocular surface toxicity



Fig. 7 Munson sign

5 Tear Dysfunction

In the general population, the prevalence of tear dysfunction ranges from 11 to 26%, with onset often occurring in those over 50 years of age [35, 36]. Because tear dysfunction is a common complication of AKC, it may present at a younger age in AD patients [26, 37]. ‘Dry eye’ symptoms include burning, stinging, and foreign body sensation [38]. Management of underlying AKC (Table 2), as well as the use of preservative-free artificial tears, typically improves symptoms. AKC patients with tear dysfunction have an increased risk of squamous metaplasia [39].

6 Cataracts

The overall incidence of cataracts in AD patients is approximately 5–38% [40]. AD of even mild severity is associated with cataract development before the age of 50 years [4]. The risk of developing atopic cataracts in childhood is quite low, and may have been exaggerated in past reports; however, children with AD are at an increased risk of cataract development, which may require surgical treatment, compared with those without AD [41]. AD is considered a risk factor for the formation of posterior (PSCs) and anterior subcapsular cataracts (ASCs). Although ASCs are uniquely more specific to AD, PSCs are more common overall [40] and may occur in AD as an adverse effect of corticosteroid use [26]. However, the association between cataracts and AD pre-dates the development of corticosteroids for AD treatment [42, 43].

Interestingly, a recent population-based Korean study found other forms of atopy, but not AD, were associated with cataracts [44].

The etiology of cataracts in AD remains unclear. It is hypothesized that cataract formation may be related to disease severity [4, 40], facial distribution of AD lesions [45], chronic inflammation and oxidative stress [46], repeated facial rubbing and scratching leading to breakdown of the

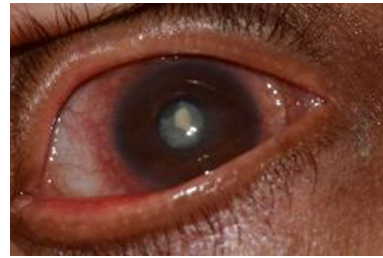


Fig. 8 Anterior subcapsular cataract

blood–aqueous barrier [47–49], genetic predisposition [50, 51], and corticosteroid use [40]. Other studies have found a lack of association with corticosteroid use, AD skin involvement, and serum IgE levels [52–54]. Proposed risk factors for ASC include infantile AD and family history of atopy [40].

Classically, ASC in AD are bilateral, shield-shaped opacities in the anterior cortex that develop rapidly, within months (Fig. 8) [40]. Cataracts may be asymptomatic or present with impaired vision, glare, photophobia, or monocular diplopia. Fundoscopic examination shows loss of the red reflex. One-third of patients with ASC also exhibit signs of atopic external eye disease, such as conjunctivitis or keratitis [21]. Treatment of ASC is usually surgical.

7 Retinal Detachment

AD patients are at increased risk of spontaneous retinal detachment, even without a previous diagnosis of AKC [11, 52]. In healthy patients, retinal detachment typically occurs in a bimodal age distribution, with the largest incidence above 60 years of age, and a smaller peak in highly myopic patients aged 20–30 years. However, AD patients typically develop retinal detachment in the second and third decades of life [47]. Most reports of retinal detachment in AD patients come from Japan, where up to 11.4% of AD patients experience this condition [45, 55–58]. Incidence rates may be lower in Europe and the US [59] and may have decreased in recent years [60]. In AD patients, retinal detachment is more likely to occur bilaterally (19% vs. 7% in patients without AD) [60, 61].

Retinal breaks or tears may be asymptomatic, but increased floaters, flashes of light, or a ‘curtain’ falling over the peripheral visual field should prompt urgent ophthalmologic evaluation. Without treatment, retinal detachment may progress to permanent vision loss.

Risk factors of retinal detachment include facial and periocular AD involvement [59]. Overall, 47–89% of AD patients with retinal detachment have comorbid cataracts [45]. AD patients are also at increased odds of myopia

[62], a known risk factor for retinal detachment, and should receive regular vision screening.

While the pathogenesis of retinal detachment in AD is largely unknown, mechanical trauma is commonly implicated [14]. Patients with chronic eye rubbing behavior frequently have an increased risk of retinal detachment [45]; retinal tears in AD patients commonly affect the retina's temporal side, suggesting scratching from the ipsilateral hand [14]. Other prominent theories suggest there is a connective tissue defect intrinsic to AD that predisposes these patients to retinal detachment [21].

Patients with small, peripheral, macula-sparing retinal detachment can be treated with laser photocoagulation or cryotherapy, whereas larger areas of involvement may require pars plana vitrectomy [63].

8 Glaucoma

In the setting of atopy, glaucoma is usually associated with an increase in corticosteroid-induced IOP, resulting in irreversible optic nerve damage [64]; this is an open-angle type of glaucoma. The concept of intrinsic atopic glaucoma has been recently proposed as a new clinical entity [65, 66]. Glaucoma in the setting of atopy may be treated with either IOP-lowering medications or surgery. AD patients are at higher risk for postoperative ocular complications due to the associated eyelid and ocular surface inflammation [65].

9 Bacterial Blepharoconjunctivitis

Atopic patients have increased susceptibility to superinfections due to dysregulation of the skin barrier and immunity [67, 68]. *Staphylococcus aureus* colonizes 67% of individuals with AD versus 6% without [69]. In AD, blepharoconjunctivitis is most commonly caused by *S. aureus* bacterial colonization in the conjunctivae and eyelid margins [69, 70]. Typically, the organism is spread to the eyes from the fingers by frequent rubbing and itching [69]. Staphylococcal blepharitis (Fig. 9) presents with crusting, redness, and thickened, hyperemic lid margins, as well as small flaky scales around the lash roots. Madarosis, trichiasis, and eyelid ulcerations are possible sequelae [70, 71]. Treatment involves eyelid hygiene, ophthalmic antibiotics, or, rarely, systemic antibiotics.

10 Herpetic Eye Disease

Several studies have reported an association between AD and herpetic eye disease, a significant cause of sight-threatening infection [72, 73]. In a study of 114 atopic patients



Fig. 9 Staphylococcal blepharitis

with ocular herpes simplex virus (HSV), AD patients had a fourfold increased risk of developing ocular HSV [72]; with two or more atopic conditions, the odds were ninefold higher. AD patients presented with more severe ocular HSV, and had twice the odds of having herpes zoster ophthalmicus (HZO) compared with those with other atopies [72]. The proposed rationale for the association is dysfunctional cell-mediated immunity and impaired skin barrier [37].

Ocular HSV infection is sometimes referred to as ocular eczema herpeticum (EH) and most commonly presents as keratitis [72, 74–76]. Herpetic keratitis may occur in atopic patients irrespective of the presence of EH, and may occur alternately or simultaneously with AKC [77]. The characteristic painful, pustular herpetic vesicles on the eyelid margin may not be present in ocular HSV, but, if present, warrant urgent referral to ophthalmology for prophylactic treatment of keratitis [37, 74, 78]. Although not pathognomonic, bilateral corneal HSV is often a clinical indicator of atopic eye disease [37]. Branching dendritic lesions of the cornea are considered a pathognomonic finding of corneal epithelial herpetic disease, although herpes may affect all levels of the cornea and even the retina. HSV-1 is more commonly implicated than HSV-2. Definitive diagnosis is obtained from polymerase chain reaction or culture. The differential diagnosis also includes AKC and secondary microbial keratitis due to bacterial colonization. Management entails prompt use of systemic and sometimes topical antiviral agents, as well as corneal evaluation [75, 79]. Long-term oral antiviral prophylaxis is highly recommended for patients with a history of HSV keratitis because it decreases recurrence rates and potential vision loss from cornea scarring [80].

11 Uveitis

Uveitis is intraocular inflammation. Although case reports have suggested an association [81–83], a recent large case–control analysis argues against a substantial influence of AD on uveitis onset [84]. In this study, the uveitis case cohort and the control cohort did not differ significantly in history of AD [84]. Despite this, uveitis secondary to HSV or varicella zoster virus may occur more frequently since AD patients are

at higher risk for these infections compared with those without disease [72].

12 Conclusions

Eyelid and eye surface inflammation is common in AD patients and may cause significant vision loss if untreated. Chronic atopic disease may result in AKC, cornea ulceration, secondary infections, keratoconus, corneal perforation, cataracts, and retinal detachment. These findings suggest a need for providers to proactively inquire about symptoms and risk factors for ocular disease, and, when appropriate, to recommend evaluation by an ophthalmologist.

In our review, we outline a ‘pre-referral approach’ for dermatologists, which includes taking an ocular review of symptoms, including eye pain, itching, discharge and vision changes. We remind dermatologists to look for and ask about eye-rubbing behavior and to inquire about a pre-existing ocular history of glaucoma. Additionally, we review gross examination findings that dermatologists may identify, such as conjunctiva injection, atopic eyelid changes, and Munson’s sign. We stress the importance of referring to ophthalmology, especially with corticosteroid treatments, because many ocular complications require specialized examination.

AD patients with acute eye pain and vision loss should be referred immediately for ophthalmologic evaluation. Patients with severe AD, but without the concerning symptoms of eye pain and vision loss, should be referred, on a non-urgent basis, to an ophthalmologist for baseline eye examination, screening and management of AKC, dry eye, keratoconus, keratitis, cataracts, ocular infection, suspected corneal or retinal involvement, and glaucoma. As with other systemic co-morbidities of AD, ocular diseases require a multidisciplinary approach. With awareness of these conditions and prompt referral, dermatologists can play a pivotal role in the prevention of potentially sight-threatening ocular complications.

Compliance with Ethical Standards

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Conflict of interest Kristen M. Beck, Gerami D. Seitzman, Eric J. Yang, and Isabelle M. Sanchez have no conflicts of interest to declare. Wilson Liao has a research grant with Sanofi/Regeneron, which manufactures dupilumab. Sanofi/Regeneron was not involved in the content, writing, or review of this manuscript.

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