Recalcitrant Atopic Keratoconjunctivitis in Children: A Case Report and Literature Review

Jing Li, MD, Xiaohui Luo, MD, Hongmin Ke, MD, Lingyi Liang, MD, PhD

abstract

Atopic keratoconjunctivitis (AKC) is the most severe type of allergic conjunctivitis and may eventually lead to blindness. Although AKC is reported to be more prevalent in adults, we report a child with AKC whose clinical characteristics were not inconsistent with those typically seen in adult patients with AKC, and who was refractory to traditional topical anti-inflammatory and immunosuppressant therapies. An 11-year-old boy presented with a 3-month history of ocular redness and itching and decreased vision for a week in both eyes. Slit-lamp examination revealed typical signs of vernal keratoconjunctivitis, including cobblestone papillae in both upper conjunctiva, superficial punctate keratopathy on the right cornea, and a sterile shield-shaped ulcer on the left cornea. Physical examination revealed eczematous lid changes and a generalized body rash, particularly on the face, neck, and flexor surfaces of the limbs. He was diagnosed to have AKC in both eyes and atopic dermatitis. The patient did not respond well to conventional topical antihistamine, mast cell stabilizers, corticosteroids, or tacrolimus, even in combination with amniotic membrane transplant. After using systemic immunosuppressants, the symptoms were relieved; the inflammation on the skin and ocular surface subsided, the cobblestone papillae disappeared, and the corneal ulcer healed gradually within 8 weeks. This case reveals that pediatric AKC should be differentiated from vernal keratoconjunctivitis because both disorders include upper cobblestone papillae, but the former is accompanied by atopic dermatitis. Pediatric AKC requires appropriate and aggressive treatment to prevent sight-threatening corneal complications. Systemic immunosuppressant should be considered when traditional topical anti-inflammatory therapies have failed.

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Dr Li designed the case report, collected data, drafted the initial manuscript, and revised the manuscript; Drs Luo and Ke collected data and revised the manuscript; Dr Liang conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Allergic conjunctivitis is one of the most common ocular conditions and its incidence has increased dramatically in recent decades. It can be classified into 5 types, including seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis, vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). Of these, AKC is considered to be the most severe form and is characterized by atopic dermatitis (AD), conjunctival cicatrization, symblepharon, and various corneal disorders that may eventually lead to blindness.[1] Atopy affects 5% to 20% of the general population, and AKC occurs in 20% to 43% of individuals with AD.[2,3] According to the literature, AKC is prevalent in adults and uncommon in children.[4] Here, we report a child with AKC whose clinical characteristics were not inconsistent with traits

typically seen in adults with AKC, and who was refractory to traditional topical immunosuppressants.

CASE REPORT

An 11-year-old boy presented with a 3-month history of ocular redness and itching and decreased vision in both eyes for a week. He had been previously diagnosed as having vernal conjunctivitis in both eyes, but did not respond well to topical mast cell stabilizers, antihistamines, or fluorometholone 0.1%. He did not wear contact lenses. His medical history was unremarkable except for AD and allergic rhinitis. His mother has allergic asthma.

His visual acuity was 20/100 in both eyes. External examination revealed eczema, erythematous rashes on the eyelids, thickened lid margins in both eyes, and ptosis affecting the left eye (Fig 1A). Slit-lamp examination revealed conjunctival injection, cobblestone papillae, and follicles in both upper tarsal conjunctiva (Fig 1B). Superficial punctate keratitis was noted in the right cornea and a shield-shaped ulcer measuring 6 × 7 mm was noted in the left cornea (Fig 1C). Other ocular examinations were unremarkable. Physical examination revealed severe periorbital erythema with excoriations and generalized rashes on the body, particularly on the face (Fig 1D), neck, and flexor surfaces of the limbs.

In vivo confocal microscopy revealed apoptotic cells in the superficial epithelium and dendritic cell infiltration underneath the epithelial layer in both eyes (Fig 2). The serum immunoglobulin E level was markedly elevated (>2500 IU/mL; normal <120 IU/mL) and the eosinophil percentage was also markedly increased to 20% (normal 0.5%–5%). Skin tests showed hypersensitivity to dust mite, beef, and pollen.

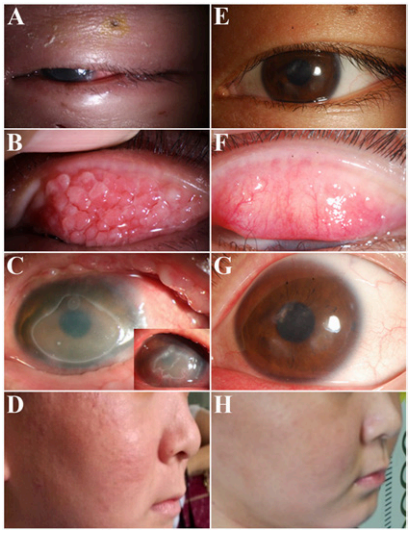

FIGURE 1
External and slit-lamp photographs. A, Note the eczematous lids; B, the giant papillae on the upper lids; C (and inset), the cornea shield ulcer that worsened after AMT; and D, the facial eczema. E and F, After treatment, the ocular inflammation and papillae subsided; G, the cornea ulcer healed; and H, the skin became less inflamed.

The patient was started on topical immunosuppressant eye drops tacrolimus 0.1% (Talymus; Senju Pharmaceutical Co, Ltd, Osaka, Japan) twice daily, a combination of mast cell stabilizer and antihistamine eye drops olopatadine hydrochloride (Patanol; Alcon Co, Ltd, Fort Worth, TX) twice daily, corticosteroid eye drops fluorometholone 0.1% (Flumetholon; Santen Pharmaceutical Co, Ltd, Osaka, Japan) 4 times daily, an antibiotic levofloxacin (Cravit; Santen Pharmaceutical Co, Ltd) 4 times daily, and artificial tears sodium hyaluronate 0.3% (Hialid; Santen Pharmaceutical Co, Ltd) 4 times daily, with a bandage contact lens applied to the left eye. After 3 weeks of treatment, the condition in neither eye improved and the shield ulcer worsened. Delayed healing of such lesions may result in corneal scarring and a decrease in vision. To protect the cornea against the mechanical rubbing insult from the giant papillae on the upper lid, promote healing, and suppress the inflammation, amniotic membrane transplant (AMT) was performed uneventfully on the left eye, as reported in the treatment of a noninfectious corneal ulcer, including AKC.[5,6] Postoperatively, the membrane was covered by a bandage contact lens. The topical anti-inflammatory and immunosuppressant regimens were continued after AMT. The membrane dissolved 10 days postoperatively, at which time, the papillae were persisting, and the corneal ulcer was worsening, with progressive vascularization (Fig 1C inset).

Because the patient did not respond to the above-mentioned conventional topical immunosuppressant treatment, we initiated systemic immunosuppressant therapy, comprising oral tacrolimus capsules (PROGRAF; Astellas Pharmaceutical Co, Ltd, Killorglin, County Kerry, Ireland) at a dose of 4 mg per day, methotrexate tablets (Methotrexate; Sine Pharmaceutical Co, Ltd, Shanghai Shi, China) 12.5 mg per week, and prednisone acetate tablets (Prednisone; Sine Pharmaceutical Co, Ltd), 40 mg per day, gradually tapered to 10 mg per day. After systemic treatment, the eyelid (Fig 1E) and ocular surface inflammation decreased significantly, the giant papillae gradually subsided (Fig 1F), and the corneal epithelial defect healed with faint scarring within 6 weeks (Fig 1G). The patient's vision improved to 20/30 in the right eye and 20/40 in the left eye. The rash on the face and body was also significantly improved (Fig 1H). All oral medications were continued through the 10-month follow-up. No systemic side effects or recurrence was noted during follow-up.

DISCUSSION

AKC was first described by Hogan[3] in 1952 as a severe ocular complication of AD, but was almost forgotten by the ophthalmic community for half a century.[2] Foster and Calonge[1] then

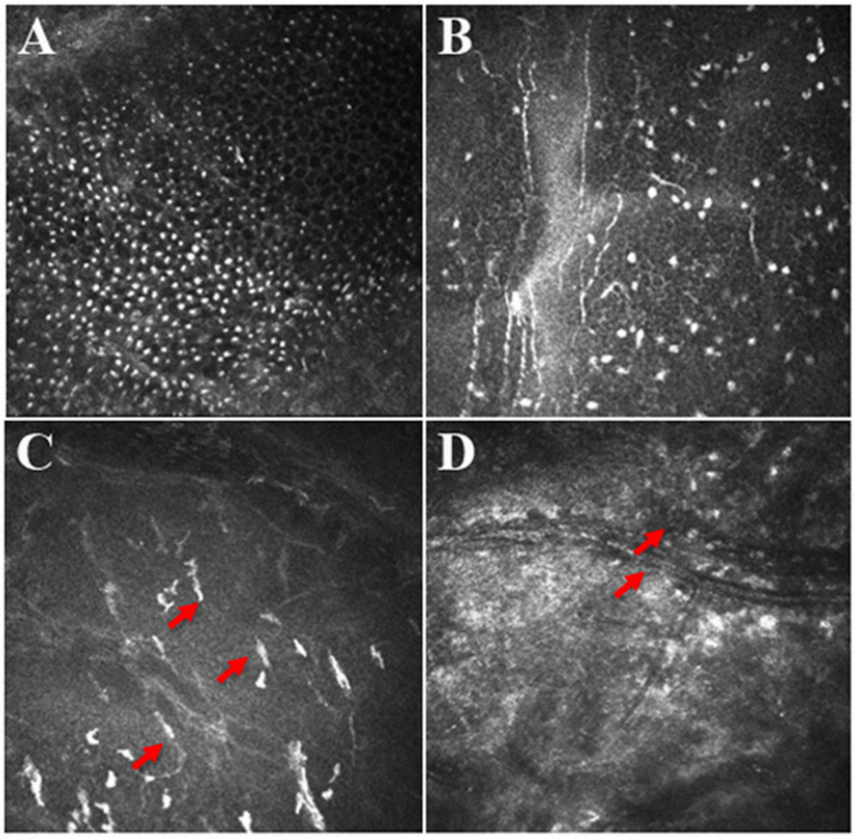

FIGURE 2
In vivo confocal microscope examination of the left cornea. A and B, Note the lymphocyte infiltration in the epithelial and subepithelial layers; C, infiltration of dendritic cells (arrows); and D, neovascularization (arrows).

reported a series of 45 patients with severe ocular surface involvement and a background of AD in 1990. The seriousness of AKC, including the high prevalence of severe blepharitis, conjunctival scarring, persistent corneal epithelial defects, and the increased risk of secondary infections, which often result in visual loss and even blindness, has not been sufficiently emphasized.[7,8] Patients often have symptoms of ocular irritation, including itching, redness, tearing, pain, and blurred vision.[7–11]

AKC has been defined as a chronic inflammation of the ocular surface that patients with atopy may suffer at any time during the course of their atopic disease and independent of its degree of severity.[9] Historically, AKC has rarely been recognized as a diagnostic entity before puberty and is thought to occur predominantly in adults. There is no unified global diagnostic criterion for AKC, so it is difficult to study this disease, especially in children. In Japan, patients with keratoconjunctivitis and any history of AD are diagnosed with AKC, regardless of age.[10] However, in Europe, only patients beyond the age of puberty presenting with concurrent keratoconjunctivitis would be diagnosed as having AKC.[11] In 2015, Brémond-Gignac proposed the diagnostic criterion of pediatric AKC as the presence of severe allergic conjunctivitis with AD that is diagnosed before 16 years of age.[12]

VKC is another rare but severe type of allergic conjunctivitis that may involve the cornea. Severe itching and cobblestone papillae are the most significant characteristics of VKC, and thus have diagnostic value. Brémond-Gignac reported the largest series of pediatric AKC, which included 23 patients.[12] Most clinical features in that case series overlapped with those of VKC,[12] as documented in our case. The presence of AKC-related clinical features but an absence of VKC-related clinical features in combination with a history of eczema and conjunctivitis and/or keratitis may secure an accurate diagnosis of AKC in children.[12] However, if a pediatric patient presents with typical clinical features of VKC, distinguishing AKC from VKC is challenging. For example, our patient had ocular redness and itching, conjunctival injection, cobblestone papillae on the conjunctiva of the upper lid, and a shield ulcer, which are the typical manifestations of VKC and explain why the patient had been previously misdiagnosed as having VKC. The poor response to topical immunosuppressants and the presence of AD prompted us to make a diagnosis of AKC according to the criteria of Brémond-Gignac[12] and the Japanese diagnostic criteria for AKC.[13]

Differentiating AKC from VKC in children is important. VKC is self-limiting with a generally favorable prognosis, but may have seasonal recurrences or exacerbation. The course of VKC lasts from 2 to 10 years[14] and resolves without significant loss of vision.[15] In contrast, AKC is chronic, progressive, and perennial, and may persist into the fourth and fifth decades of life. AKC tends to have a poor prognosis because it may be complicated by failure of the ocular surface and intraocular complications, such as cataract and retinal detachment. Therefore, early diagnosis, treatment, and lifelong follow-up of AKC are important, especially when the condition develops in childhood.[16–18] Similarly, an ophthalmic consultation is needed when a patient with AD presents with ocular discomfort.[19]

The key feature that helps to distinguish pediatric AKC from VKC is AD. However, the cutaneous changes of AD might be located in areas that are covered by clothes, such as flexor surfaces of the arms and legs, which might be overlooked by the ophthalmologist.

It is worth noting that the clinical features in our pediatric patient with AKC were not completely in conformity with those of typical adult-onset AKC, which usually manifests as subconjunctival infiltration and cicatrization in the lower lid rather than the upper lid,[20] whereas the giant papillae were concentrated on the upper lid in our pediatric patient. We suggest that the clinical characteristics and even the pathologic process involved in childhood-onset and adult-onset AKC may be different. The underlying mechanism of AKC in the different age groups remains unclear.

The ocular and cutaneous inflammation of AKC and AD is mediated by type I and type IV hypersensitivity reactions.[21] T cells, B cells, and mast cells play critical roles in the pathogenic mechanism of AKC. The management of AKC requires a multidisciplinary approach.[16] Conventional therapies include avoidance of allergens,[22] use of topical mast cell stabilizers, antihistamines, and corticosteroids.[8,22] Tacrolimus is a strong immunosuppressant that can suppress proliferation of T-cell and B-cell proliferation,[4,23] as well as block degranulation of mast cells.[4,24,25] Previous studies have revealed that topical use of tacrolimus significantly improves the ocular signs and subjective symptoms of severe AKC and VKC within 2 weeks.[24,26] In addition, the amniotic membrane (AM) has been shown to have anti-inflammatory effects and promote healing. Furthermore, when AM tissue is secured onto the corneal surface using a 10-0 nylon running suture (so-called AMT), it protects the cornea against mechanical rubbing by the giant papillae on the upper lids when blinking. Therefore, for patients with a corneal ulcer complicated by AKC, AMT may be highly effective as previously reported.[27,28] Use of a "nonsecured" AM such as ProKera (Biotissue Inc, Doral, FL), which is an AM draped over a large plastic ring that is placed on the eye like a contact lens, has been reported in the treatment of noninfectious keratitis. This is easily performed in the office, and the AM and ring remain in place for 1 to 2 weeks until the AM dissolves, after which the ring is removed, which can also be performed in the office.[29] Furthermore, the giant papillae can occasionally be surgically removed in conjunction with an autologous conjunctival graft or AMT, which can also accelerate the healing process of a shield ulcer.[30,31] Most patients with AKC respond well to the above-mentioned topical therapies. In a few studies, authors have reported the use of systemic immunosuppressant therapy, including oral cyclosporine and tacrolimus, in patients with refractory AKC, and corticosteroid, methotrexate, azathioprine, and mycophenolate mofetil for patients with recalcitrant AD.[17,32] However, all reports have so far been in adult patients. Here, we report the first successful use of systemic immunosuppressant therapy, including prednisone and methotrexate, in a pediatric patient with AKC whose ocular and dermal inflammation persisted after 3 months of topical immunosuppressant therapy.

CONCLUSIONS

AKC is a rare but severe chronic ocular complication of AD. Clinical features of pediatric AKC may resemble those of VKC but differ from adult AKC, so there is a risk of misdiagnosis. Unlike VKC, AKC is progressive and may be complicated by loss of vision, so early diagnosis and prompt treatment are particularly important. Careful examination of the skin and identification of AD are key for the diagnosis of AKC. For pediatric patients with intractable AKC in whom topical treatment has failed, systemic immunosuppressants may be initiated under close monitoring.

ABBREVIATIONS

AD: atopic dermatitis
AKC: atopic keratoconjunctivitis
AM: amniotic membrane
AMT: amniotic membrane transplant
VKC: vernal keratoconjunctivitis

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