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Ocular Surface Squamous Neoplasia Associated with Atopic Keratoconjunctivitis

Ankit Shah[a] Edgar M. Espana[a, b] Arun D. Singh[c, d]

[a]Department of Ophthalmology, Cornea and External Disease, University of South Florida, [b]Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, [c]Department of Ophthalmic Oncology, and The Cole Eye Institute and [d]Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio, USA

Key Words
Neoplasia · Atopia · Ocular surface · Masquerade · Inflammation

Abstract
Purpose: To describe 2 cases of invasive squamous cell carcinoma that originated in the setting of severe atopic keratoconjunctivitis (AKC). ***Methods:*** Case one involved a 73-year-old male with atopic eczema and severe AKC who developed a limbal lesion suspicious for ocular surface squamous neoplasia (OSSN). Slit-lamp examination was significant for a new sessile lesion in the temporal limbal region of the left eye. The lesion was treated with excisional biopsy and cryotherapy. Topical therapy with mitomycin C, topical interferon alpha 2b, and topical 5-fluorouracil provided only partial control. Exenteration was eventually needed. Case two involved a 53-year-old male with history of severe AKC and eczema. Computed tomography imaging showed an infiltrative mass of the right orbit. Incisional biopsies confirmed conjunctival squamous cell carcinoma of both sides (invasive in the right eye, in situ in the left eye). Exenteration was needed for control of invasive carcinoma in the right eye. ***Results:*** Squamous cell carcinoma was treated without success in spite of surgical excision and aggressive treatment with multiple topical agents and multiple applications of cryotherapy. Orbital exenteration was needed in both cases. ***Conclusion:*** Chronic inflammation associated with AKC may be a risk factor for the development of bilateral, diffuse, invasive, and recurrent OSSN that may require exenteration.

Introduction

Atopic keratoconjunctivitis (AKC) is a subtype of ocular allergy characterized by eyelid eczema and varying degrees of ocular surface inflammation that progresses to conjunctival subepithelial fibrosis, limbal stem cell deficiency, and symblepharon formation [1, 2]. Lid involvement may cause cicatricial changes, ectropion, and madarosis. It is a chronic and bilateral condition and commonly follows a relapsing and remitting course without a seasonal predisposition, in contrast to vernal conjunctivitis [3]. Patients often have a strong family or personal history of asthma, eczema, or other atopic dermatitis. However, there are reports of patients with typical AKC findings without any concurrent atopic dermatitis but who manifest other atopic conditions [4].

E-Mail karger@karger.com
www.karger.com/oop

Arun D. Singh, MD
The Cole Eye Institute and Taussig Cancer Center, Cleveland Clinic
2022 East 105th St.
Cleveland, OH 44195 (USA)
E-Mail singha@ccf.org

Table 1. Published cases of OSSN developing in the setting of AKC

Reference	Eyes/ patients	OSSN type	Treatment	Recurrence
Heinz et al. [12]	6/10	In situ 2, invasive 4	Excisional biopsy, amniotic membrane transplantation, oral mucosa transplants, local radiotherapy	none
Kallen et al. [13]	6/7	In situ 2, invasive 4	Excisional biopsy, topical mitomycin C, local radiation, exenteration in one case	one case of recurrence
Schmack et al. [14]	1/1	Invasive	Excisional biopsy, cryotherapy, amniotic membrane transplantation	none
Gericke et al. [15]	4/2	Invasive and in situ	Excisional biopsies, amniotic membrane transplantation, topical mitomycin C	yes, 3 times in one case
Current case	3/2	Invasive and in situ	Excision, mitomycin C, interferon, fluorouracil, cryotherapy	yes, multiple
Total	20/22		Mitomycin C, cryotherapy/excision, interferon	yes

Both type 1 and type 4 hypersensitivity reactions have been confirmed as a contributing factor in the pathogenesis of AKC [5]. Conjunctival biopsy specimens reveal extensive admixture of eosinophils, mast cells, Th1 and Th2 helper cells suggestive of an abnormal response from the adaptive immune system in predisposed individuals [6].

The major risk factors for ocular surface squamous neoplasia (OSSN) include exposure to sunlight, smoking, immunosuppression, and infection from human papilloma virus subtypes 16 and 18 [7]. Only a few cases of OSSN developing in the setting of AKC have been reported (table 1) [8–11]. Herein, we report 2 cases describing unique clinical characteristics and recalcitrant course of OSSN associated with AKC.

Case Reports

Case 1

A 73-year-old white male with several years' history of bilateral atopic keratoconjunctivitis and failed penetrating keratoplasty for aphakic bullous keratopathy in the left eye, bilateral open-angle glaucoma, and macular degeneration presented to the cornea clinic for routine follow-up visit. His ophthalmic medications included timolol 0.5% twice daily in the right eye, acetazolamide 500 mg oral twice a day and dexamethasone ophthalmic ointment at bedtime in the left eye.

On examination, his best-corrected visual acuity was 6/200 in the right eye and light perception in the left eye. Intraocular pressure was 18 mm Hg in the right eye and could not be obtained in the left eye. Slit-lamp examination showed madarosis in the right lower lid with associated mild inferior fornix shortening of both eyes consistent with a diagnosis of atopic keratoconjunctivitis. Furthermore, the ocular surface of the right eye was irregular with diffuse punctate epithelial erosions on staining. There was a conjunctivalized failed corneal graft in the left eye. A sessile papillomatous-like lesion was noted in the temporal limbus of the left eye (fig. 1a, b). The anterior chamber was quiet and deep in the right eye and could not be detailed in the left eye due to the failed corneal graft. Bilateral aphakia was noted. The lesion was suspicious for malignancy.

The patient was assessed in conjunction with the oculoplastics and ophthalmic oncology services and an excisional biopsy with cryotherapy using a double freeze thaw technique was applied to all involved areas. Histopathology confirmed a clinical diagnosis of conjunctival intraepithelial neoplasia with severe dysplasia without invasive disease and negative margins (fig. 1c, d). Because of suspicion for diffuse surface involvement, adjuvant topical 0.04% mitomycin C for four cycles [8] (1 week on and 1 week off) was administered with a follow-up every 2 weeks. At the end of the 4th cycle, there was total resolution of ocular surface disease by slit-lamp examination (fig. 2a, b). The patient complained of excessive dryness, redness, itchiness and irritation that worsened with each treatment cycle, and in presence of excellent response, it was decided to discontinue mitomycin C.

At the 3-month follow-up, areas suspicious for recurrent tumor were noted on the ocular surface (fig. 2c, d). The patient underwent repeat cryotherapy using a traditional double freeze thaw technique in the areas of recurrence without further excision as most of the conjunctiva appeared scarred. Cryotherapy was performed in 3 separate occasions for areas of recurrence. Recurrences of suspicious squamous cell carcinoma were also noted in the left upper eyelid and in the inferior limbus, which required a left upper eyelid excisional biopsy with reconstruction and additional cryotherapy. Biopsy of the upper eyelid confirmed squamous cell carcinoma with negative margins; however, the inferior limbal lesion could not be biopsied. Topical interferon alpha 2b, 1 million units/ml, was used 4 times a day for 2 weeks in the left eye. Because of the persistent tumor at the left eye inferior limbus, a decision was made to discontinue the interferon. Subsequently, topical 1% 5-fluorouracil 4 times a day was used for 3 cycles each of 1 week

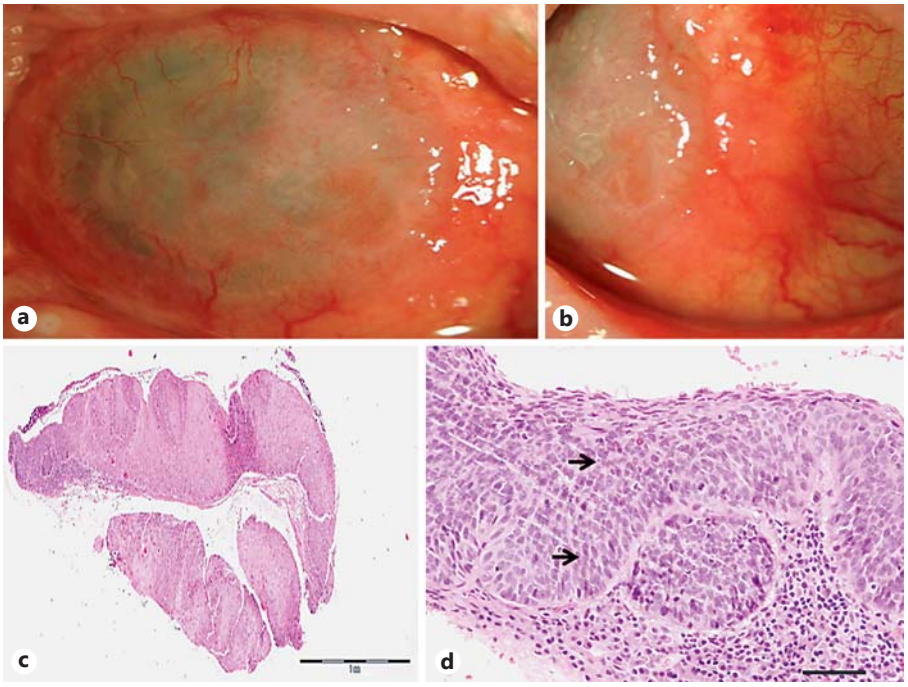

Fig. 1. Initial presentation of OSSN. A sessile papillomatous-like lesion was noted in the left eye in an eye with a previous penetrating keratoplasty (**a**). The lesion was located in the temporal limbal area (**b**). Excisional biopsy showed dysplastic cells suggestive of intraepithelial neoplasia that did not penetrate basement membrane and was graded as severe dysplasia (**c**). Dysplastic cells were noted at higher magnification. No keratinization was noted (**d**).

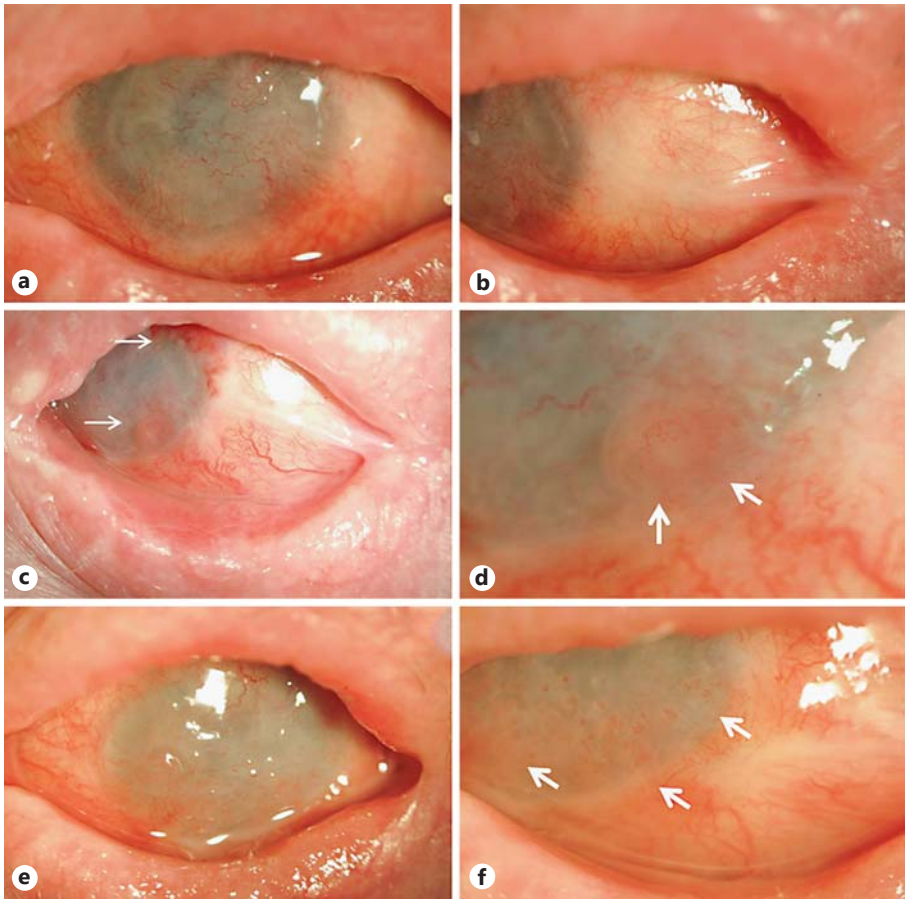

Fig. 2. Signs of tumor recurrence 3 months after completion of 4 cycles of topical mitomycin C chemotherapy. Three different areas suspicious for tumor recurrence were noted (**a–c**). Higher-magnification picture shows a papillomatous area that is highly suspicious for recurrence (**d**). Diffuse areas of recurrence invading into the corneal surface after aggressive treatment with multiple therapeutic modalities (**e**). Higher magnification shows recurrent frond-like lesions in the inferior corneal surface (**f**).

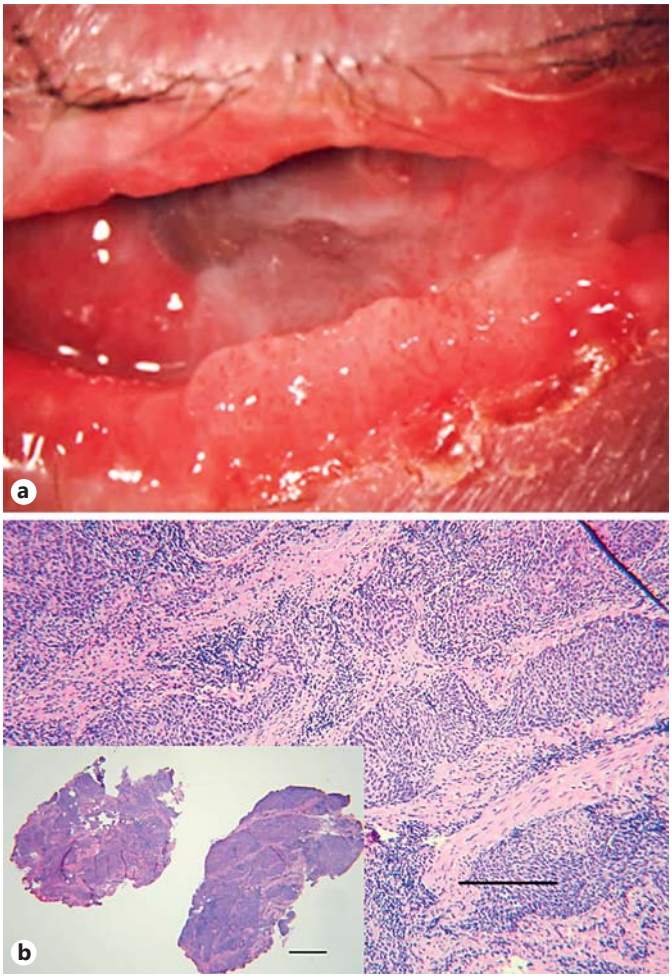

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Fig. 3. Initial presentation of patient with right eyelid lesion illustrating large papillomatous lesion with erythema, ulceration, and loss of lashes (**a**). Right eyelid excisional biopsy shows sheets of invasive epithelium and connective tissue typical of invasive squamous cell carcinoma (**b**).

duration. The eye appeared to be free of tumor at the 2 months of follow-up. However, new areas of recurrence were noted 3 months after discontinuation of 5-fluorouracil (fig. 2e, f). The patient was reluctant to undergo exenteration and additional cryotherapy was used without success. The patient ultimately required and underwent a lid-sparing exenteration of the left orbit without any complications.

Case 2

A 53-year-old male with past medical history significant for chronic atopic dermatitis, and eczema presented to the cornea service for evaluation of chronic eye irritation. Given his substantial atopic disease, the patient was previously treated with systemic steroids and photochemotherapy (PUVA). He subsequently developed a cataract in the left eye and had uncomplicated cataract extraction with intraocular lens implant. His previous ophthalmic history included steroid-responsive open-angle glaucoma, blepharoconjunctivitis, and a mild right eye cataract. The patient began to develop progressive right-sided proptosis and retroorbital pain in the subsequent years prior to presentation.

Visual acuity in the right and left eye was hand motion and 20/30, respectively. Intraocular pressure was not obtainable in the right eye and 11 in the left eye. External evaluation of the right eye depicted a papillomatous ulcerative lesion measuring 2 cm on the lower eyelid with associated thickening, erythema and madarosis of the lid margin (fig. 3a). Extraocular movements were preserved, and there was mild proptosis of the right eye. Slit-lamp examination illustrated a large gelatinous, vascular inferior perilimbal lesion with diffuse opacification and conjunctivalization of the cornea in the right eye. The patient also had a suspicious elevated, white lesion with fronds in the conjunctiva between 7 and 8 o'clock of the perilimbal region of the left eye (fig. 4a, b). Given the corneal condition of the right eye, an evaluation of the anterior chamber and fundus was limited.

There was high suspicion for both a malignancy of the conjunctiva and lid in the right eye, and of the conjunctiva in the left eye. The patient was initiated on tobradex ointment twice daily in both eyes. Computerized tomography scan of the orbits revealed a homogenous soft tissue density mass located in the superior-lateral and inferior aspects of the right orbit abutting the infero-lateral and superior aspects of the globe. There was involvement of the superior rectus, lateral rectus, inferior oblique, and inferior rectus muscles as well as the lacrimal gland.

The patient underwent a right orbitotomy with biopsy of the right upper and lower eyelid, conjunctiva and orbit as well as left conjunctival biopsy. Results revealed invasive squamous cell cancer of the right orbit and upper and lower palpebral conjunctiva (fig. 3b). The left conjunctiva biopsy showed squamous cell cancer in situ (fig. 4c, d). The patient agreed to undergo right orbit exenteration. The lesion in the left eye responded well and resolved with the use of topical interferon dosed at 1 million units/ml four times a day for 6 months but recurred 3 months after discontinuation of topical interferon (fig. 4e, f).

Discussion

Our experience indicates that severe, uncontrolled atopic keratoconjunctivitis is a potential risk factor for development of OSSN that is bilateral, diffuse, invasive, and recurrent. Our two cases add to the few reports in the current literature that suggest an association between AKC and OSSN. Heinz et al. [12] and others [13–15] have reported patients with OSSN associated with atopic eczema from Germany (table 1). To our knowledge, there are no such reports from other parts of the world.

Links between cancer and inflammation were first made in the nineteenth century, based on observations that tumors often arose at sites of chronic inflammation and that inflammatory cells were present in tumor tissue [12]. For instance, it is believed that chronic inflamma-

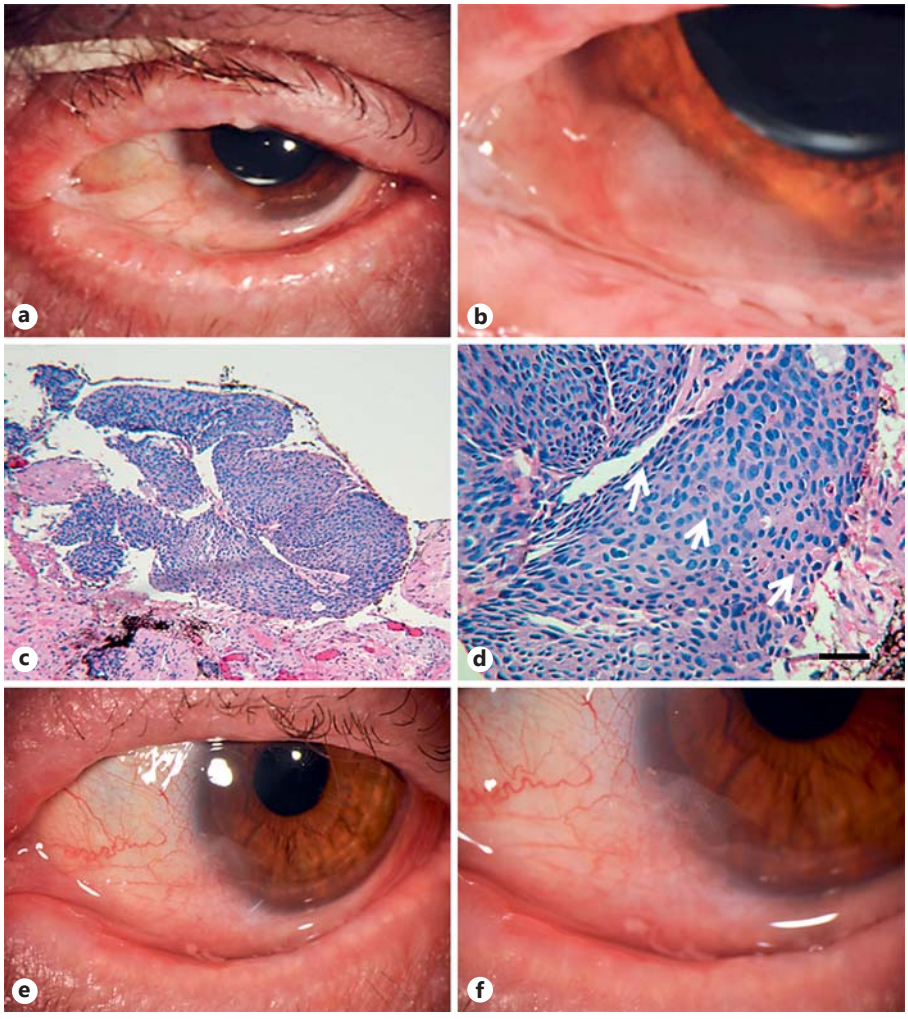

Fig. 4. Left eye conjunctival lesion located near the perilimbal region at 7 o'clock with mild elevation, vascularity and nodularity (**a**). Higher-magnification photo confirms raised, friable lesion (**b**). Histopathology illustrates cellular atypia, and diffuse dysplasia of the surface epithelium without invasion into the basement membrane (**c**, **d**). The lesion in the left eye responded well and resolved with the use of topical interferon dosed at 1 million units/ml four times a day for 6 months but recurred 3 months after discontinuation of topical interferon (**e**, **f**).

tion plays a significant role in the development of cervical, stomach, and head and neck squamous cell cancers [13, 14]. Additionally, human papillomavirus and human immunodeficiency virus infection is a known risk factor for OSSN [7, 15, 16]. It is unclear whether immunosuppression, inflammation or coinfection with HPV play a role in pathogenesis [16].

It is well known that AKC is associated with chronic ocular surface inflammation with the main inflammatory effector cells being mast cells, T cells, eosinophils and conjunctival cells [17] and patients with AKC have lower levels of IgA in their tears that may predispose them to chronic infections and inflammation [18]. An association between AKC, chronic inflammation, and squamous metaplasia has been reported in previous studies. Dogru et al. [17] performed impression cytology in a Japanese series of patients and showed loss of goblet cells and the presence of squamous metaplasia in patients with AKC.

Inflammatory cells such as neutrophils, monocytes, macrophages, and eosinophils provide mediators, including various cytokines, chemokines, and free radicals, that lead to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis [19, 20]. We hypothesize that chronic inflammation occurring in atopic keratoconjunctivitis could lead to onset and relentless progression of OSSN. The poor response to traditional conservative treatments and the high incidence of recurrences are likely attributed to persistently elevated inflammatory markers in AKC.

In conclusion, our cases illustrate that chronic inflammation associated with AKC may be a risk factor for the development of bilateral, diffuse, invasive, and recurrent OSSN that may require exenteration.

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Statement of Ethics

The study complied with the guidelines for human studies and animal welfare regulations. The subject gave informed consent and the study protocol was approved by the institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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