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CASE REPORT

Ocular surface squamous neoplasia in a setting of fungal keratitis: a rare co-occurrence

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Abstract
Purpose To describe a rare co-occurrence of ocular surface squamous neoplasia (OSSN) in a patient with microbial keratitis.
Methods Case report.
Results We describe a 68-years female who developed ocular surface squamous neoplasia (OSSN) in an eye with culture proven severe fungal keratitis of 5 months duration, which progressed to endophthalmitis. She was managed with extended enucleation for left eye. Histopathology examination was consistent with squamous cell carcinoma of ocular surface with no corneal stromal/scleral/anterior chamber involvement. She received adjuvant chemotherapy with topical Interferon alpha2b (3 cycles) for positive margins. Sixmonths after treatment, she is completely tumor free.
Conclusion Co-occurrence of OSSN and chronic fungal keratitis is rare. We recommend that patients with chronic ocular infections should be examined and followed closely for abnormally thickened limbal areas.

Keywords Ocular surface squamous neoplasia · OSSN · Keratitis · Fungal keratitis

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Ocular surface squamous neoplasia (OSSN) commonly presents as a papillomatous, leukoplakic, gelatinous or nodular growth over ocular surface straddling the limbus, with no associated clinical signs of inflammation [1]. Etiology of OSSN has been linked to viral infection and immunosuppression, but direct cause–effect relationship has not been established yet [2, 3]. A relentless OSSN with multiple recurrences has been reported in atopic keratoconjunctivitis with history of chronic topical cyclosporine use [4]. Heinz et al. [5] reported an association of OSSN with atopic eczema in 6 cases where immunologic alteration was speculated to be the underlying factor. Chronic topical steroid usage has been linked to OSSN in a series of transplanted cornea [6]. We describe an unusual presentation of OSSN in a chronically infected ocular surface. To the best of our knowledge, similar association has not been reported before.

Case summary

A 68-year-old female presented to ocular oncology services with a non-healing corneal ulcer of 5-month

duration. Her best corrected visual acuity (BCVA) was light perception, left eye and 6/9, right eye. She had no history of systemic immunosuppression/diabetes mellitus or chronic smoking. Screening of HIV by ELISA method was negative. Systemic examination was unremarkable. She had developed pain and redness in left eye after a trivial trauma, 5 months ago. At presentation, her slit lamp microscopy showed deeply infiltrated central and paracentral cornea with exudates in anterior chamber, which showed fungal hyphae on KOH mount (Fig. 1a). She was started on 5% topical natamycin, 1% voriconazole one hourly and systemic ketoconazole along with mydriatics. Records report no limbal lesion at presentation (Fig. 1b). Some signs of improvement were noted, but no complete resolution occurred at any point of follow-up. She had refused to the option of therapeutic keratoplasty and hence was kept on topical natamycin 6td and oral ketoconazole. At 5 months from presentation, her slit lamp examination revealed a papillomatous lesion measuring 7 × 3 mm extending from 1'o clock to 5'o clock straddling limbus with the presence of keratin and feeder vessels (Fig. 1c, d). Excessive pigmentation started developing circumferentially around the limbus. There was no regional lymphadenopathy. Repeat KOH microscopy demonstrated fungal filaments. Her vision has reduced to inaccurate projection of rays in left eye with vitreous echoes on ultrasonography.

With clinical diagnoses of pseudo-epitheliomatous hyperplasia (PEH) or OSSN, incisional biopsy was performed. Histopathology examination of the incisional biopsy was compatible with squamous cell carcinoma in situ. UBM showed no anterior chamber involvement. Considering potentially painful blind eye with vitreous exudates and surface malignancy, she was managed with left eye extended enucleation with PMMA implant. Conjunctival peritomy included 4 mm of clear margins around the lesion, followed by double-freeze thaw cryotherapy to the conjunctival edges. Ocular surface reconstruction was completed with amniotic membrane to prevent forniceal shortening. Histopathology examination revealed a central corneal ulcer with stromal thinning and mild degree of acute inflammatory infiltrates in the posterior stroma (Fig. 2a). There were thick suppurative exudates and necrosis in the anterior chamber. The peripheral corneal and conjunctival epithelium was thickened and showed atypical squamous cells involving full thickness of epithelium and invading the conjunctival stroma superficially as broad tongues (Fig. 2b). Conjunctival stroma and episcleral tissue showed mild to moderate degree of chronic lympho-mononuclear cell infiltration. The lateral and inferior resected

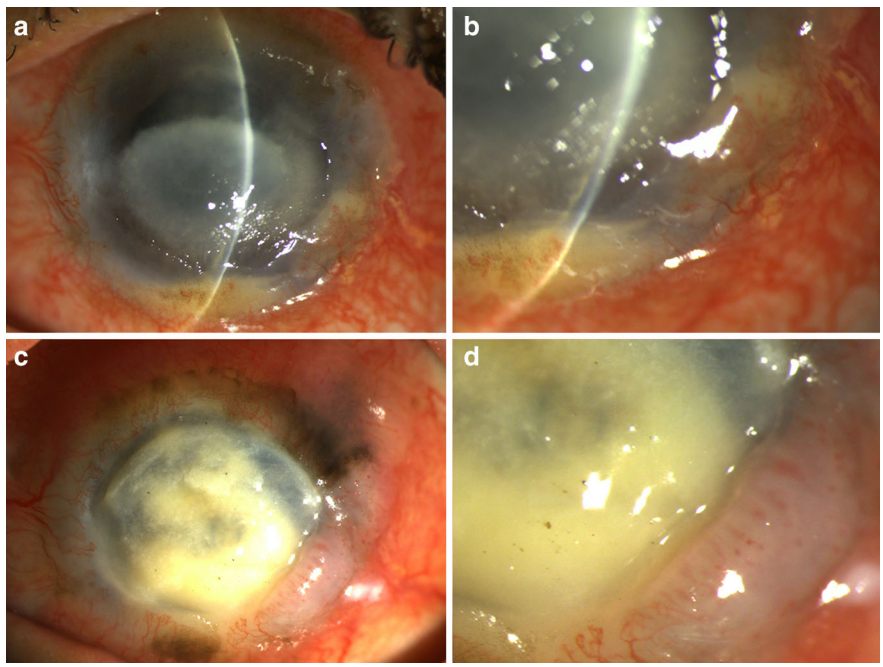

Fig. 1 **a** Diffuse corneal stromal infiltrates with ciliary congestion; **b** No discernible lesion visible at limbus; **c** after one month, 7 × 3 mm raised papillomatous lesion can be seen extending for 4 hours along temporal limbus; **d** higher magnification (40×) shows papillary fronds with adjacent keratin

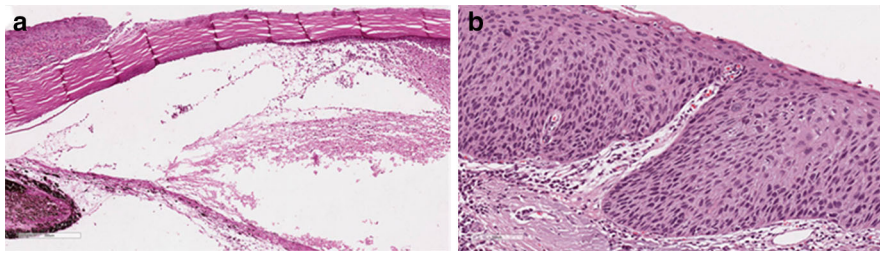

Fig. 2 **a** Photomicrograph shows a central corneal ulcer with stromal thinning and thick anterior chamber exudates (periodic acid Schiff's stain; 8×); **b** photomicrograph shows an abnormally thickened conjunctival epithelium, replaced by atypical squamous cells. Stroma shows mild degree of chronic lymphomononuclear cell and plasma cell infiltration (hematoxylin and eosin stain; 20×)

conjunctival margins showed severe dysplasia. There was no evidence of corneal stromal/scleral/intraocular involvement by tumor. Routine and special stains for fungus did not reveal any fungal organisms. She was administered 3 cycles of topical interferon alpha 2b as adjuvant chemotherapy. There were no recurrences noted at 6 months of follow-up.

Discussion

We report a rare presentation of papillomatous OSSN in a chronically inflamed ocular surface infected with fungal keratitis. Therapeutic keratoplasty should be avoided in such cases along with prompt aggressive management of OSSN.

Current case had severe fungal keratitis extending into anterior and posterior chamber. Long-standing fungal keratitis and drug toxicity due to antifungals were responsible for chronic inflammation. Long-term antifungals are usually required for treating fungal keratitis. Toxicity of topical antifungals on corneal and conjunctival epithelium in the form of non-healing epithelial defect has been reported before. Their laboratory evaluation in human corneal epithelial sheets revealed reduced cell viability and decreased healing ability of epithelial cell line [7]. Cell of origin in OSSN is postulated to be limbal basal stem cells. Normally, limbal basal cells maintain a quiescent phase but an insult to ocular surface initiates the cell cycle which predisposes to metaplasia [8]. Clinically apparent OSSN appeared at 5 months from presentation. The plausible explanation could be the presence of a small subclinical limbal lesion to begin with, which progressed to clinically visible OSSN over subsequent follow-ups. Long-standing inflammation and drug toxicity might have possibly triggered the aberrant proliferation of basal stem cells, which were otherwise quiescent but harboring damaged DNA. On retrospective evaluation of slit lamp images, we observed slightly more thickened limbal areas temporally compared to nasal limbus, corresponding to the site of papillomatous lesion, which developed later. Role of inflammation in malignancy has been evaluated in mice experiments. Predisposition to cancer in chronic inflammatory states like post-burn and venous ulcers has been reported for several skin cancers. Briso et al. [9] studied skin tumorigenesis after inducing expression of c-fos in adult mice, which resulted in CD4 T cell recruitment, epidermal hyperplasia and ultimately preneoplastic lesions. No such correlation or speculation has been reported for OSSN.

There is scarce literature on occurrence of OSSN in the setting of an inflamed ocular surface. Flynn and colleagues had described a case of forniceal conjunctival papillomatous lesion, diagnosed as OSSN on histopathology in a patient with atopic keratoconjunctivitis [4]. Resolution was achieved with topical MMC. Ramasubramanian and colleagues reported 4 cases of OSSN after corneal grafting, where use of topical steroids (local immunosuppression) was postulated to be the predisposing factor [6]. Another differential diagnosis thought of was pseudo-epitheliomatous hyperplasia (PEH). PEH a benign lesion may also develop, in chronic inflammatory conditions like vernal conjunctivitis, and post-allogeneic limbal stem cell transplantation [10]. Histologically PEH is represented as a hyperplastic stratified squamous epithelium with no evidence of dysplasia. It usually presents as a whitish nodular mass lesion with a hyperkeratotic surface. In current case, typical papillary fronds within the lesion with the presence of

feeder vessels and dysplasia on histopathology helped in distinguishing OSSN from PEH. Chronic inflammation could have possibly affected the limbal basal stem cell homeostasis, initiating limbal hyperplasia, metaplasia and further progression to dysplasia. Definite cause–effect relationship cannot be ascertained; however, it stresses the need for close follow-up of any suspicious areas in such scenario.

In conclusion, co-occurrence of OSSN and chronic fungal keratitis is rare. Old age, chronic ocular surface inflammation and OSSN in the absence of any other definite predisposing factors make our case unique. Authors recommend that patients with chronic ocular infections should be examined and followed closely for abnormally thickened limbal areas.

Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interests.

Informed consent Proper informed consent was obtained for data usage.

References

1. Shields CL, Chien JL, Surakiatchanukul T et al (2017) Conjunctival tumors: review of clinical features, risks, biomarkers, and outcomes–the 2017 J. Donald M. Gass Lecture. Asia Pac J Ophthalmol 6:109–120
2. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ (2014) Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res 129:172–182
3. Shields CL, Ramasubramanian A, Mellen P et al (2011) Conjunctival squamous cell carcinoma arising in immunosuppressed patients (organ transplant, human immunodeficiency virus infection). Ophthalmology 118:2133–2137
4. Flynn TH, Manzouri B, Tuft SJ (2012) Ocular surface squamous neoplasia in an immunosuppressed patient with atopic keratoconjunctivitis. Int Ophthalmol 32:471–473
5. Heinz C, Fanihagh F, Steuhl KP (2003) Squamous cell carcinoma of the conjunctiva in patients with atopic eczema. Cornea 22:135–137
6. Ramasubramanian A, Shields CL, Sinha N et al (2010) Ocular surface squamous neoplasia after corneal graft. Am J Ophthalmol 149:62–65
7. Kimakura M, Usui T, Yokoo S et al (2014) Toxicity of topical antifungal agents to stratified human cultivated corneal epithelial sheets. J Ocul Pharmacol Ther 30:810–814
8. Cotsarelis G, Cheng SZ, Dong G et al (1989) Existence of slow-cycling limbal epithelial basal cells that can be preferentially stimulated to proliferate: implications on epithelial stem cells. Cell 57(2):201–209
9. Briso EM, Guinea-Viniegra J, Bakiri L et al (2013) Inflammation-mediated skin tumorigenesis induced by epidermal c-Fos. Genes Dev 27(18):1959–1973
10. Mortada A (1964) Pre-epitheliomatous and pseudo-epitheliomatous hyperplasia of eyelid, conjunctiva and cornea. Am J Ophthalmol 58:813–819