Asian J Ophthalmol. 2014;14:031-035

Isolated corneal squamous cell carcinoma in a patient with unilateral dry eye symptoms

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Abstract: *The aim of this study was to report a case of isolated corneal squamous cell carcinoma in a patient with unilateral dry eye symptoms. The case was a 48-year-old man with a history of thermal corneal injury on his left eye two years ago with decreased visual acuity and dry eye symptoms a short time after, which was treated for dry eye and had no improvement in symptoms. Examination revealed hypertrophy of near total corneal epithelium, without limbal and conjunctival involvement. The surface of the lesion was irregular with punctate epithelial erosions. The patient underwent excisional biopsy which revealed severe corneal dysplasia (carcinoma in situ). After excision, the patient was treated with Fluorouracil and there was no sign of recurrence till the time of the last follow-up examination six months after excision. Dry eye symptoms had disappeared completely. We conclude that, in the case of unilateral chronic dry eye which was resistant to the treatment with signs of corneal epithelial involvement, isolated corneal neoplasia should be considered even without limbal or conjunctival involvement.*

Key words: *Isolated corneal squamous cell carcinoma, cornea, dry eye*

Introduction

Corneal and conjunctival dysplasia and squamous cell carcinoma form a wide range of squamous neoplasia and together represent the most common tumor of the ocular surface.[1] Although various terms have been used to describe the disorder, ocular surface squamous neoplasia (OSSN) describes both intraepithelial dysplasia and squamous cell carcinoma of the cornea and conjunctiva.[2] Squamous lesions of the cornea and conjunctiva are uncommon; however, they are important because of their potential for causing ocular and even systemic morbidity and mortality. The clinical presentation of these lesions extends across a wide spectrum and differs based on the degree of pathologic involvement. The cause of OSSN is unclear and possibly multifactorial. This tumor is usually unilateral and often occurs in fair-skinned men in their mid-60s who have had a history of long-term sun exposure.[3] Ultraviolet (UV) light-induced mutations to the p53 tumor suppressor gene may play a role in this condition. In addition, other identified risk factors include heavy smoking, previous exposure to petroleum derivatives, xeroderma pigmentosum, and human papilloma virus (HPV). HPV has been identified in both benign (types 6, 8 and 11) and malignant (types 16 and 18) conjunctival epithelial growths. Because

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of a possible association, human immunodeficiency virus (HIV) testing is advised in patients younger than 50 years in whom OSSN is diagnosed. Isolated squamous cell carcinoma of cornea is very rare. To the best of our knowledge, only a few such reported cases have been found in litrature.[4,5] However, most of the reported cases in aforementioned cases involve the limbus. In this case report, a case of isolated squamous cell carcinoma of the cornea without involvement of the limbus was investigated.

Case report

The reported case was a 48-year-old man with fair skin complained of the dry eye symptoms, and decreased visual acuity of his left eye. His past medical history was unremarkable. He mentioned a corneal thermal injury to his left eye two years ago and the symptoms started one month after then. With the diagnosis of the dry eye syndrome, he was treated with non-preservative artificial tear frequently, however, had no improvement of the symptoms.

At the final exam three months before referring to our specialized eye clinic, best corrected visual acuity (BCVA) was 10/10 and counting fingers at three meters in his right and left eyes, respectively. At slit-lamp examination of the left eye, epitheliopathy and filamentary keratopathy involving large areas of the cornea without limbal and conjunctival involvement was documented.

At the first follow-up examination in our clinic (Khatam-al-Anbia Eye Hospital), BCVA was 10/10 and counting fingers at six meters in his right and left eyes, respectively. Slit-lamp examination revealed hypertrophy of near total corneal epithelium with distinct and scalloped border, without limbal and conjunctival involvement (Fig. 1).

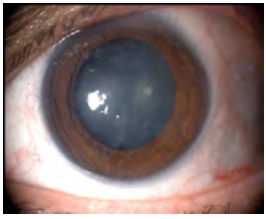

Fig. 1. Corneal epithelial hypertrophy with near total corneal surface involvement which has definite and scalloped border without involving the limbus.

The surface of the lesion was irregular with punctate epithelial erosions. Tear meniscus was normal in both eyes. Tear break-up time (TBUT) was ten and four seconds in his right and left eyes, respectively. There was no significant meibomian gland dysfunction. Other exams including ocular movements, relative afferent papillary defect (RAPD), intraocular pressure (IOP) and fundus examination were unremarkable in both eyes. Slit-lamp examination of the right eye revealed normal findings.

The patient underwent excisional biopsy (debridement) of the corneal epithelium. The smear and culture results of corneal specimen were negative for bacteria, fungi and amoeba. Histopathological investigation revealed severe corneal dysplasia including cells with irregular and hyper-chromatic nuclei and dyskeratosis

with diffuse mitosis on the entire epithelium. There was not any sign of underlying stromal involvement (Fig. 2).

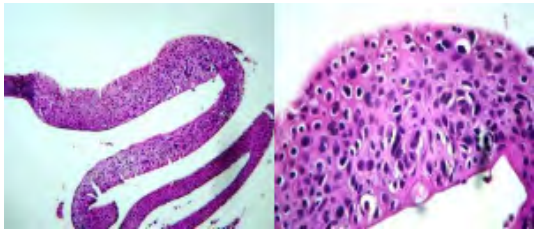

Fig. 2. Carcinoma *in situ*: Right: Severe dysplasia with cytonuclear atypy, involving full thickness of epithelium (H&E stain, x 100); Left: Cytonuclear atypy (H&E stain, x 400).

After excision, the patient was treated with Fluorouracil drop 50 mg/dl QID for two pulses of two weeks duration with one week pause between them. There was no sign of recurrence till the time of the final follow-up examination (45 days after the surgery). At the final examination, the visual acuity on his left eye was 9/10 and dry eye symptoms were disappeared completely (Fig. 3).

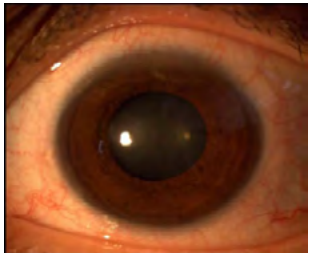

Fig. 3. Slit photograph of involved eye at last visit, with no sign of recurrence.

Discussion

Isolated squamous cell carcinoma of cornea is very rare and only few cases have been reported in the litrature.[4,5] Corneal intraepithelial neoplasia (CIN) is associated with the same risk factors as conjunctival intraepithelial neoplasia and presumably shares the same pathogenesis.

Corneal OSSN lesions typically are pre-invasive and appear as an opalescent ground-glass sheet with mottled surface. A main feature of many corneal lesions is that they have sharply defined and fimbriated borders and are avascular. Less frequently, the edges may be ragged or even smooth. The convex leading edge spreads away from the corneoscleral limbus in an advancing arc. In addition, fine white dots are often present over the gray epithelium. These lesions can sometimes appear as large, elevated, pearl-white mounds. Corneal OSSN lesions are slightly elevated in comparison with the adjacent normal epithelium. Rose bengal staining produces a diffuse punctate stain over the gray sheet. The virulence of these corneal lesions themselves is low. Early involvement of the cornea adjacent to a conjunctival lesion may manifest as a mild opacification of the cornea. Such areas have dysplastic corneal epithelium with a polycystic appearance which are best visualized by retro-illumination.[6] The etiology of these lesions is controversial, with some authors having proposed a *de novo* dysplastic process in the cornea,[7] while

others have suggested a centripetal sliding of subsequently neoplastic cells from the limbus.[8] These lesions are typically indolent and slow growing. They have a high tendency to recur.[7-9] Corneal neovascularization does not typically occur, which helps to differentiate CIN lesions from limbal stem cell failure.

The reported case in this study was a middle-aged man without any risk factors for OSSN, except the fair skin. It should be noted that thermal burn is a well-defined risk factor for squamous carcinoma of the skin, mouth and esophagus; however, there was no documented relation between OSSN and the thermal burn. Therefore, in our case, we could not state that either the thermal burn was the cause of corneal OSSN or it was a random relationship. In addition, one case of squamous cell carcinoma of the cornea and conjunctiva following thermal burn of the eye has been reported previously.[10] To the best of our knowledge, no other case of unilateral corneal SCC with initial presentation of dry eye symptoms has been reported in the literature. In the abovementioned case report,[10] the corneal schema demonstrated some signs of corneal surface squamous carcinoma. However, what mislead the mind from initial diagnosis was patient's younger age, lack of powerful risk factors, sparing of limbal and conjunctival area, symptoms and signs of dry eye specially filamentary keratopathy and lower tear break up time (TBUT) and higher incidence of dry eye than SCC.

In the ocular structure, there is a natural contraction between the tear film and the corneal surface epithelium. Any defect in the tear film or corneal epithelium could lead to filamentary keratitis. Disruption of the ocular surface epithelium is an important risk factor for filament formation which is produced by sliding of the epithelial cells around small areas of focal degeneration of the epithelium. Therefore, observation of filamentary keratopathy should not mean dry eye in any case, especially in the atypical cases such as this unilateral dry eye syndrome. This problem causes misleading of the diagnosis in our case; however, some factors helped an initial diagnosis such as: case gender, unilateral involvement, appropriate tear meniscus, the epithelial opacity and resistance to proper dry eye treatments.

Various treatment options have been previously discussed such as surgical excision with a two- to three-millimeter free margin, cryotherapy, brachytherapy, chemotherapy with mitomycine, 5- Flourouracil and interfrone α. Based on the current clinical experience, it is clear that mitomycin and 5-FU are effective options for complete eradication of pre-invasive OSSN. Use of 5-Flourouracil in the treatment of squamous carcinoma *in situ* was first introduced in 1986. This drug was used successfully with the dose of four times daily for one month in the treatment of squamous carcinoma *in situ* without combination of other therapeutic modalities.[11]

In this case study, we performed excisional biopsy of corneal epithelium for the diagnosis and treatment of the lesion. Almost all dysplastic lesions involving conjunctiva or cornea also involve the corneoscleral limbus, as this junction has the greatest mitotic activity, though isolated cases have been reported.[5,12] Although our patient had no limbal involvement, it is possible that the original abnormal cells had their origin at the corneoscleral limbus and subsequently became neoplastic after migration to the central cornea. Therefore, we have decided to treat the

patient with 5-Flourouracil (two pulses of two weeks duration with one week pause between them) after excision.

Conclusion

In the case of unilateral chronic dry eye which is resistant to the treatment with signs of corneal epithelial involvement (opacity and increasing corneal thickness), isolated corneal neoplasia should be considered even without limbal or conjunctival involvement.

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