Recurrence of invasive squamous carcinoma of the ocular surface requiring penetrating therapeutic sclero-keratoplasty

Tova E. Mannis, MD1, Mark J. Mannis, MD, FACS1, George J. Harocopoulos, MD2, Bobeck S. Modjtahedi, MD1, Jennifer Li, MD1
1. Department of Ophthalmology & Visual Science, University of California, Davis Health System Eye Center.
2. Department of Ophthalmology & Visual Sciences and Department of Pathology & Immunology, Washington University, St. Louis.
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ABSTRACT

Purpose: We review a case of invasive squamous cell carcinoma invading the cornea to discuss optimal management.

Methods: Observational case report with histopathologic analysis.

Results: Histopathology demonstrates corneal invasion by the tumor that appears to have been completely excised with a large therapeutic keratoplasty and adjuvant cryotherapy.

Conclusions: Successful management of ocular surface squamous neoplasia (OSSN) requires removal of identifiably abnormal tissue without disruption of normal protective architecture, careful histopathologic analysis, and the employment of adjuvant therapy at the time of or subsequent to surgical excision.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) is a relatively rare entity. However, in the elderly population, squamous lesions are the most common tumors of the ocular surface. Typically, OSSN presents as an exophytic, pearly grey lesion with increased surrounding vascularity, and its gross topography generally falls into one of three categories: leukoplakic, gelatinous, or papilliform. Invasive OSSN penetrates the epithelial basement membrane and spreads into the stromal tissue. Rarely, intraocular invasion can occur, and the lesion may spread into Schlemm’s canal, the trabecular meshwork, the anterior chamber, the iris, the ciliary body, and the choroid. Presumably due to the resistance of the Bowman’s layer, however, invasion by squamous cell carcinoma (SCC) occurs virtually exclusively in extra-corneal portions of the lesion barring any surgical interventions. We present an unusual case of recurrent invasive squamous cell carcinoma that moved from the limbus to dissect the corneal stroma leaving the corneal epithelium intact.

CASE REPORT

A 58 year-old man was referred to the University of California Davis Eye Center with the history of a conjunctival tumor in the left eye that was first noted by the patient one year prior to initial presentation with steady growth. The tumor was excised at an outside facility in May 2010. At that time a sclerectomy was also performed but adjuvant cryotherapy was not used. The pathology report from that procedure demonstrated well-differentiated, squamous cell carcinoma with tumor present at the deep biopsy margins. The referring physician requested an evaluation to determine the next best steps in treating residual tumor.

The patient was seen one month after his initial tumor excision. Visual acuity was 20/25 in the right eye and 20/60 in the left eye. Examination of the left eye revealed a 6.5mm (vertical) x 4.5mm (horizontal) area temporally that appeared to represent the location of excision. The area was not inflamed and was epithelialized except for a small area inferiorly. Hyperemic conjunctiva and conjunctival scarring surrounded the excision site. The intraocular pressure was 18 mm Hg in the left eye.

Given the history of positive margins, as seen in the original pathology report, the use of topical chemotherapy with Mitomycin C was recommended. The referring physician was encouraged to employ lubricating ointment to facilitate epithelial healing after which a two-week cycle of mitomycin would be undertaken. The patient returned to the care of the referring ophthalmologist.

In September 2010, four months after the patient’s original surgery, he returned for follow-up. The treating...
physician had noted an enlarging corneal opacity in the left eye and, due to concern for possible infectious keratitis, initiated antibiotic drops. He had not, however, employed topical chemotherapy as recommended. The patient was then referred back to UC Davis.

At this visit, visual acuity was 20/25 in the right eye and counting-fingers at 2 feet in the left eye. There was a temporal area of edematous and inflamed conjunctiva with dilated episcleral vessels and an area of leukoplakia adjacent to the temporal limbus. There was also a large, dense stromal opacity in the temporal cornea with evidence of corneal neovascularization and overlying microcystic epithelial changes. There was no epithelial defect. This corneal opacity extended into the visual axis. Intraocular pressure was 29 mm Hg in the left eye (Figure 1).

Ultrasound biomicroscopy revealed a large solid mass lesion (9.95mm x 8.23mm x 2.4mm) extending into the cornea dissecting the corneal stroma. There was no clear evidence of invasion into the anterior chamber. We could not rule out possible ciliary body involvement. We elected to proceed with a large corneal-scleral graft with the application of cryotherapy. The patient was informed of the high-risk nature of this procedure including potential loss of the eye.

All abnormal-appearing conjunctiva was excised with 3 mm margins and submitted for pathology. In addition two specimens were submitted as “mapping” biopsies. Two rounds of overlapping cryotherapy application (freeze/thaw/freeze) were performed to encircle the entire area of the tumor in the cornea and sclera. The limbal portion of the lesion was excised in lamellar fashion, dissecting down to the base of invasion and excising the abnormal conjunctiva temporally. Since the lesion appeared to invade deeply into the stroma, the decision was made to perform penetrating sclero-keratoplasty in order to ensure complete removal of tumor while also maintaining globe integrity. Accordingly, a 10 mm full-thickness, eccentric trephination was performed to include the residual limbal/scleral bed temporally, extending to trabecular meshwork, as well as all abnormal cornea.

The nasal portion of the cornea was left in place. A donor corneal-scleral graft was sutured into place using 9-0 nylon sutures. The conjunctival defect was then closed to cover bare sclera using Vicryl sutures.

Three weeks post-operatively, the patient’s vision in the left eye was counting-fingers at three feet. Examination revealed mild hyperemia, a clear corneal graft with sutures in place, a formed anterior chamber, and an intraocular pressure of 18. Two months post-operatively, the graft remained clear with well-controlled IOP. Visual acuity was counting fingers due to a cataract. There were no clinical signs of recurrence of the tumor (Figure 2). The graft remained clear at 18 months with no evidence of recurrence of tumor.

HISTOPATHOLOGIC FINDINGS

Sections of the limbal portion of the lesion from the patient’s left eye showed invasive squamous cell carcinoma extending to the base of the lamellar dissection (Figure 3). Surface keratinization correlated with the leukoplakia seen clinically. A chronic inflammatory response was present in the stroma. The temporal margin appeared free of neoplasia. The corneo-scleral button, encompassing all abnormal cornea along with the residual scleral bed beneath the aforementioned lamellar dissection, contained the remainder of the squamous carcinoma, emanating from the temporal area of invasion and dissecting along the mid- to deep corneal stroma, without involvement of the overlying corneal epithelium. The squamous
carcinoma did not extend to either the nasal edge of excised cornea or to the temporal edge of sclera, indicating a complete excision. The deep margin was clear, with no intraocular tumor extension. The conjunctival mapping biopsies were also negative for neoplasia. Accordingly, the lesion was staged as T3 as per the AJCC classification.4

DISCUSSION

Invasive OSSN often begins in the conjunctiva and extends across the limbus to involve the superficial adjacent cornea. Rarely does intraocular invasion occur, but to our knowledge, there are no other reports of corneal stromal extension of tumor without involvement of the corneal epithelium. Other reports document OSSN with extensive involvement of the corneal epithelium, but without corneal stromal invasion.5,6 Kafarnik and colleagues7 reported corneal stromal invasive squamous cell carcinoma in 10 horses, but in these cases there was no conjunctival or corneal epithelial involvement seen on histology. Similar cases in humans have not been identified in the literature. The authors do concede that there may have been an epithelial entrance to the stroma that was not included in the plane of the histologic sections.

One of the important factors that may prevent extension of neoplasm into the corneal stroma is the protection afforded by the Bowman layer.3 It is extremely important, when possible, to maintain an intact Bowman’s layer during the surgical excision of a superficial OSSN. It is both possible and likely that the original surgeon crossed Bowman’s layer during the resection. If the tumor has already breached Bowman’s layer, demonstration of clean surgical margins is imperative. Since the initial pathology report indicated the presence of tumor at the surgical margin, it is probable that the surgeon had not removed all of the malignant invasive tissue. Conversely, if the tumor is superficial and exophytic, which is the usual case, deep keratectomy and/or sclerectomy may not be indicated and may both compromise the integrity of Bowman’s layer or provide access to the internal eye through the aqueous veins present under the limbus.

Recurrence rates for both pre-invasive and invasive OSSN following surgical excision range from 15% to 52%. Recurrence rates are significantly lower when surgical margins are demonstrated to be histologically negative. As a result, adjunctive therapy is often considered a way to limit tumor recurrence, since clinically the margin of the lesion may not be identifiable at surgery. Sudesh et al.8 demonstrated that recurrence rates were lowered significantly when cryotherapy was applied to the tumor margins following excision. They also emphasized that both primary and recurrent tumors generally involve the limbus and, therefore, adjunctive cryotherapy to this area may be
particularly helpful in preventing recurrence. Typically, management of squamous cell carcinoma of the conjunctiva involves wide margin excision followed by freeze-thaw cryotherapy. Complications of cryotherapy include lack of selectivity between normal and abnormal tissues, iritis, corneal edema and scarring, peripheral retinal ablation, and changes in intraocular pressure.10

Similarly, topical chemotherapy with agents like mitomycin C, 5-fluorouracil, and alpha interferon-2B (alpha IFN-2B) have been effective in the treatment of recurrent and primary OSSN and may be particularly useful in the case of an excision with positive tumor margins. Sepulveda and colleagues11 found that all three agents were effective in the treatment of OSSN. They also identified the following relative indications for topical chemotherapy of non-invasive OSSN: greater than two quadrants of conjunctival involvement, greater than 180 degrees of limbal involvement, extension into the clear cornea, positive margins after excision, unsuitability of the patient for surgery. In a case series study, Chen et al.12 administered topical mitomycin C to 27 patients following OSSN excision and after a mean follow-up time of twenty-seven months, found no evidence of clinical recurrence in any of these cases. Ocular toxicity after administration of topical chemotherapeutic agents is generally limited to the duration of treatment, and in a small, prospective study Panda et al.13 demonstrated that treatment with mitomycin C had no significant effect on corneal endothelium. Nonetheless, adverse effects are more common when the these agents are applied to bare sclera with no overlying conjunctiva to provide blood flow.10 There are few randomized, prospective trials to determine the efficacy of adjuvant chemotherapy.14

The present case highlights the potential for corneal stromal dissection by SCC following deep, incomplete conjunctival tumor excision without adequate adjunctive cryotherapy or topical chemotherapy. In general deep sclerectomy is neither necessary nor desirable in most cases of OSSN, which is commonly exophytic, slow growing and non-invasive in the presence of normal anatomic barriers. Presumably in our case, there was already invasion of the stroma at the time of the original presentation based on the pathology report. This patient had a successful corneal-scleral graft following removal of residual tumor, but the procedure posed significant long-term risks. Successful management of OSSN requires removal of identifiably abnormal tissue without disruption of normal protective architecture, careful histopathologic analysis, and the employment of adjuvant therapy at the time of or subsequent to surgical excision.

REFERENCES
