Novel Insights from Clinical Practice

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Widespread Ocular Surface Squamous Neoplasia Treated with Topical Interferon Alpha-2b

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Established Facts

- Ocular surface squamous neoplasia (OSSN) is a spectrum of epithelial neoplasias that includes invasive disease.
- Treatment options for large OSSN lesions include a combination of surgical excision, chemotherapy, and immunotherapy.

Novel Insights

- Widespread OSSN lesions with circumferential limbal involvement can be solely treated with topical interferon alpha-2b. However, invasive disease must be ruled out first.

Keywords
Conjunctival intraepithelial neoplasia · Interferon alpha-2b · Ocular surface squamous neoplasia · Cytokine immunotherapy · Ocular surface

Abstract

Purpose: To emphasize the importance of staging ocular surface squamous neoplasia when contemplating use of topical interferon alpha-2b alone. ***Cases:*** Two patients with 360 degrees of limbal involvement. ***Results:*** Two patients with in situ squamous cell carcinoma of the conjunctiva and clinical involvement of the entire limbus were treated with topical interferon alpha-2b. Thorough examination and multiple biopsies excluded invasive disease. The patients had complete response to therapy. ***Conclusion:*** Widespread intraepithelial squamous neoplasia involving the entire limbus can be successfully treated with topical therapies. Biopsy plays a role in excluding invasive disease. Interferon alpha-2b is a preferable agent to start with because it is well tolerated. Since long-term risks of recurrence are unknown, appropriate monitoring is essential.

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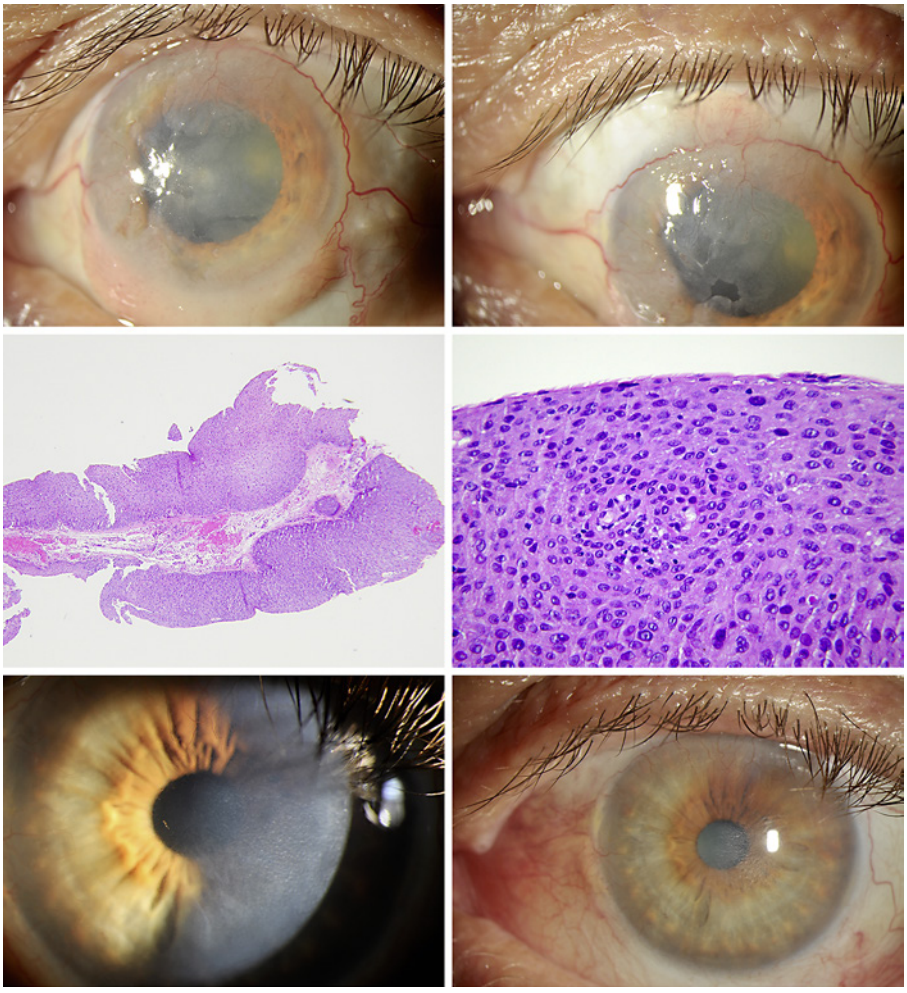

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Fig. 1. Patient 1. On initial examination, the cornea was diffusely hazy with a thick irregular epithelial surface. Conjunctiva at the limbus was thickened and pink, most easily seen between 4 and 8 o'clock, and 12 o'clock (upper left and right). Biopsy from 6 o'clock showed folds of markedly thickened epithelium replaced almost entirely by dysplastic cells, shown at low and high magnification (middle left and right). After topical therapy, the cornea regained its clarity and the limbus returned to normal (lower left and right).

Introduction

Ocular surface squamous neoplasia (OSSN) describes a range of epithelial neoplasia from intraepithelial dysplasia to squamous cell carcinoma [1]. Its causation is multifactorial but OSSN has been associated with older age, male gender, cigarette smoking, UV-B light exposure, fair complexion, HPV and HIV infections, and immunosuppression [2–5]. Depending on the clinical stage of disease, treatment options include surgical excision with or without irradiation or cryotherapy, photodynamic therapy, topical chemotherapy, immunotherapy, and antivirals [1, 6–10].

There is no universally accepted approach to treating OSSN. One recommended method for well-defined lesions is surgical excision with 3-mm margins using a no-touch technique with double freeze-thaw cryotherapy [10]. This approach, however, is not an option for advanced disease, such as those with extensive limbal involvement. Topical therapies with 5-fluorouracil [11], mitomycin-C [12], interferon alpha-2b (IFNα2b) [13], and cidofovir [8, 9] are alternatives that may be as effective as surgery for in situ disease (clinical stage Tis, American Joint Committee on Cancer Classification [14]). In select cases, topical pharmacotherapies offer several potential advantages over surgery or cryotherapy including minimizing injury to limbal stem cells [7]. Topical IFNα2b is well tolerated compared to topical antimetabolites. We present 2 cases of OSSN of the conjunctiva with circumferential involvement of the limbus. In the absence of documentable invasive disease, they were treated cautiously with topical therapies with resolution of their surface neoplasia.

Case Reports

Patient 1

An 80-year-old man with no past ocular history was referred for evaluation of progressively worsening itching, tearing, and decreased vision of his left eye for an ill-defined period. Visual acuity

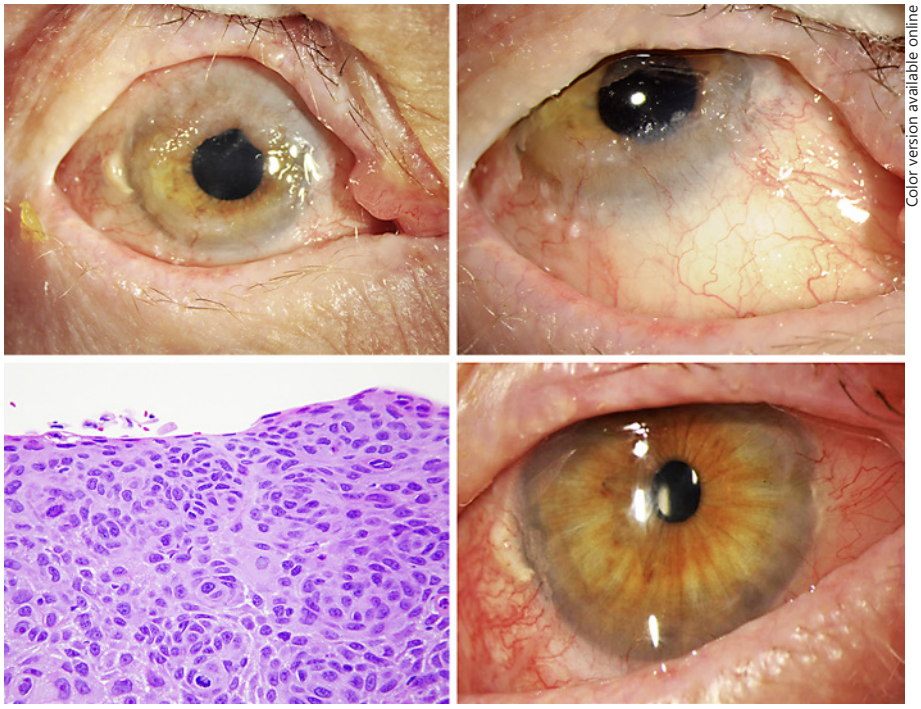

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Fig. 2. Patient 2. On initial examination, the hazy, vascularized cornea was encircled by diffusely thickened conjunctiva, worse superiorly (upper left) compared to the lower limbus (upper right). First biopsy showed severe dysplasia, shown here at high magnification (lower left). Repeat biopsies confirmed carcinoma in situ. After treatment, the cornea cleared, vessels regressed, and the conjunctival surface was normal. Mild residual chemosis and vascular injection persisted, but later resolved (lower right).

in the symptomatic eye was counting fingers at 3 feet. Examination revealed a diffusely hazy cornea with peripheral neovascularization. The conjunctiva immediately posterior to the limbus was thickened and pink, particularly between 4 and 8 o'clock and at 12 o'clock (Fig. 1, upper left and right). Incisional biopsies at the thickest areas showed severe dysplasia to carcinoma in situ (Fig. 1, middle left and right). After management options were discussed, topical IFNα2b 1 million IU/mL 4 times daily was initiated and maintained for 4 months. At 4 months, there was marked improvement in the clarity of the cornea and the conjunctiva had returned to normal (Fig. 1, lower left and right). Examination at 7 months revealed corrected visual acuity was 20/50. There were no signs of surface neoplasia.

Patient 2

An 81-year-old man with a history of basal cell carcinoma of the right upper eyelid status post complete excision, and previously treated squamous cell carcinoma of the right cheek was referred for progressive worsening vision in his right eye for 1 year. Visual acuity in the eye was 20/100. Examination showed diffusely irregular conjunctiva and cornea surfaces with extensive limbal neovascularization (Fig. 2, upper left and right). Biopsy from the most severely affected area showed squamous epithelial dysplasia with subepithelial inflammation (Fig. 2, lower left). Unsure if squamous cell carcinoma had been excluded, 6 additional map biopsies were performed. All showed carcinoma in situ. After treatment options were discussed, the patient opted for IFNα2b therapy 1 million IU/mL 4 times a day. The patient was treated for 3 months. Posttreatment exam showed clinical resolution of surface neoplasia (Fig. 2, lower right). The conjunctival surface was smooth and there was mild chemosis and injection throughout secondary to the irritative effects of immunotherapy. Nine months after completion of topical IFNα2b, there was no evidence of recurrence. Nonspecific injection and chemosis resolved. Corrected vision had improved to 20/30.

Discussion

Topical IFNα2b has been used successfully to treat so-called "giant" OSSN that involves more than 180° of the limbus [15, 16]. There have also been a few reports describing successful immunotherapy in persons with circumferential limbal involvement [6, 17]. These successes, however, need to be interpreted with an important caveat: the effectiveness of topical immunotherapy for invasive OSSN (i.e., squamous cell carcinoma) has not been established. This qualification may get lost in the discussion of OSSN, since some clinical series do not report clinical staging or depth of tumor invasion [18]. Some studies also erroneously define OSSN as in situ neoplasia, further confounding comparisons of clinical studies that include squamous cell carcinoma under the umbrella of OSSN [19]. Finally, some studies blur the role of topical treatment as an adjuvant to surgery for squamous cell carcinoma, leading some to employ it as lone therapy.

In one clinical series of 18 giant OSSN managed with IFNα2b, 17 (94%) showed evidence of squamous cell carcinoma [15]. While 72% responded to IFNα2b, patients

Table 1. Tumor staging for primary squamous cell carcinoma of the conjunctiva*

Stage	Definition	Applicable synonyms	Comment
Tis	Neoplastic proliferation confined to epithelium	OSSN; epithelial dysplasia (mild to severe); carcinoma in situ	Actinic keratosis falls under preinvasive neoplastic disease, usually displaying granular layer and keratin
T1	Invasive disease less than 5 mm in greatest diameter, and does not invade contiguous structures	OSSN; SCC	Based on definitions for invasion for T3, stages T1 and T2 are essentially restricted to the bulbar surface
T2	Invasive disease greater than 5 mm in greatest diameter, and does not invade contiguous structures	OSSN; SCC	Stages T1 and T2 invade substantia propria, and theoretically extend into sclera as it is not defined as an adjacent structure under stage T3
T3	Tumor invades adjacent structures: cornea, intraocular tissue, forniceal conjunctiva, palpebral conjunctiva, tarsus, lacrimal punctum/canaliculi, plica, caruncle, posterior lamella eyelid, anterior lamella eyelid, and/or margin of eyelid	OSSN; SCC	Stage T3 essentially encompasses SCC located anywhere outside bulbar surface of conjunctiva
T4	Tumor invades orbit with or without further extension	OSSN; SCC	Since OSSN is an umbrella term, it applies to the most advanced cases of SCC that arise on the surface of the eye
T4a	Tumor invades orbit without further extension	OSSN; SCC	
T4b	Tumor invades bone	OSSN; SCC	
T4c	Tumor invades paranasal sinuses	OSSN; SCC	
T4d	Tumor invades brain	OSSN; SCC	

* Based on guidelines created by the American Joint Committee on Cancer [14]. OSSN, ocular squamous surface neoplasia; SCC, squamous cell carcinoma.

with invasive disease required local injections and/or surgery. In another series of 10 patients with OSSN, one required exenteration likely because topical therapy delayed definitive diagnosis and treatment of squamous cell carcinoma [20]. Those authors concluded that topical IFNα2b by itself is contraindicated if invasive disease is present.

In a series of 81 cases of OSSN, 42 showed evidence of squamous cell carcinoma, some to a depth of 1 cm [21]. Although these patients had overall good outcomes, topical IFNα2b was used in combination with surgery for cases with invasive disease [21].

The extent or burden of OSSN incorporates both measurements of contiguous surface involvement and depth of invasion. This concept is captured in the general rules for cancer staging for primary tumor (T in the TNM system), which stratifies conjunctival carcinomas according to these two criteria (Table 1) [14].

Although there may be willingness to diagnose OSSN based solely on clinical examination or with impression cytology, these are less sensitive means of detecting squamous cell carcinoma than biopsy [19, 22]. Surface lesions with generous conjunctival thickening, lesions fixed to underlying tissues, symblepharon formation, or lesions with surface dimpling suggest invasive disease and call for diagnostic biopsy. New imaging modalities such as optical coherence tomography might also play a role in screening patients with OSSN for microinvasive disease [23]. It may also become a valuable tool for monitoring patients after treatment for recurrence, including occult deep tumor.

The consequence of treating unrecognized squamous cell carcinoma with topical IFNα2b is that topical therapy may successfully eradicate intraepithelial disease while leaving deep tumor free to proliferate [24]. In this situation, the resolution of surface neoplasia can mask infiltrating squamous cell carcinoma leading to a delay in

clinical recognition. Although we used map biopsies targeting areas most suspicious for invasive disease, incisional biopsy does not absolutely exclude the possibility of invasive disease. In the second patient, we harvested a second set of tissue to better exclude this possibility, since slit-lamp assessment alone can be fallible in detecting early invasion. For this reason, careful clinical follow-up, including examination for signs of intraocular spread (cell and flare, subtle mass lesions, asymmetric intraocular pressures, etc.), are necessary.

Topical IFNα2b appears to have a greater margin of safety than topical antimetabolites, which may injure conjunctival stem cells [25]. Some investigators have used topical retinoic acid in combination with topical IFNα2b for the treatment of OSSN and found that clinical effectiveness and possibly safety are improved [26]. These results need to be replicated before the role of retinoic acid can be appropriately evaluated. Another factor to consider in selecting therapy is cost. In the United States, a course of topical IFNα2b is relatively more expensive than mitomycin and 5-fluorouracil, and this cost differential varies considerably both within the United States and internationally where differences in national health care systems often impact drug prices [27–29]. Additionally, IFNα2b is compounded and requires refrigeration.

In summary, we describe 2 patients with widespread in situ carcinoma of the conjunctiva who responded to topical IFNα2b. Successful treatment with only topical therapy, however, entails exclusion of invasive disease. Clinicians need to be mindful that recurrences following topical therapy can occur beneath the epithelium if squamous cell carcinoma initially escaped detection [24]. Since the mean time for recurrence after topical therapies is roughly 17 months, with some cases appearing much later, close long-term monitoring is required [30, 31]. External slit-lamp photos might be considered at follow-up visits to help detect subtle changes overlooked on clinical examination. Biopsy should be considered if signs of surface recurrence develop.

Statement of Ethics

The patients provided consent to publish this material. The institution's Investigation Review Board on human research reviewed the protocol and approved the study.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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