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CASE REPORT

FIVE YEARS FOLLOW-UP OF CONJUNCTIVAL SQUAMOUS CELL CARCINOMA TREATED WITH ADJUNCTIVE INTERFERON ALPHA-2b

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ABSTRACT

Conjunctival squamous cell carcinoma mostly arises from the limbal stem cells of the eye. Some of the risk factors for conjunctival squamous cell carcinoma are male gender, advanced age, ultraviolet radiation, and human papillomavirus. Squamous cell carcinoma can manifest with vision loss, ocular redness, mass-feeling, and pain. We aim to present a case of conjunctival squamous cell carcinoma successfully treated with surgical excision, cryotherapy, keratectomy, partial scleral excision, and topical interferon alpha-2b. An 81-year-old male patient presented to the Trakya University Department of Ophthalmology complaining of redness and pain in his left eye. Our patient was diagnosed with squamous cell carcinoma when the pathological examination and clinical picture were reviewed together. The lesion was completely excised with the no-touch technique, and no complications were observed. Pathology specimen showed tumor-free surgical margins. Even though the surgical margins were tumor-free, due to clinical suspicion for recurrence the patient was prescribed topical interferon alpha-2b drops post-operatively and had no recurrence in 5 years of follow-up. In conclusion, although the gold standard treatment in ocular squamous cell neoplasia is still surgical excision with cryogenic therapy, topical chemotherapeutic agents can reveal a good response in the treatment of conjunctival squamous cell carcinoma.

Keywords: Conjunctival neoplasm, interferon alpha, squamous cell carcinoma

INTRODUCTION

Ocular squamous cell neoplasia (OSSN) comprises a wide spectrum of ocular surface tumors, ranging from conjunctival intraepithelial neoplasia (CIN) to invasive squamous cell carcinoma (SCC) (1). SCC due to OSSN is the most common malignancy of the conjunctiva, and OSSN is the third most common ocular tumor in the older population (1, 2). OSSN can be classified as benign, pre-invasive carcinoma in situ, or invasive SCC. These tumors predominantly occur in white male individuals of older age with a mean age of occurrence of 56 years. Populations living at latitudes closer to the equator than 30° are also at higher risk (1).

The etiology of OSSN is categorized into four important groups: increased solar ultraviolet (UV) radiation exposure, human papillomavirus (HPV), human immunodeficiency virus (HIV), and conditions predisposing the limbal transition zone to dysplasia (1-3). The direct role of HPV is still unclear in the pathogenesis of OSSN, but it can be a cofactor in susceptible hosts (2, 4, 5). Other risk factors associated with OSSN are history of skin cancer, being outdoors for more than half of the first 6 years of life, and phenotypic features such as fair skin, pale irides, and a tendency to get sunburnt when exposed to sunlight (6).

Ocular squamous cell neoplasia tends to emerge from the corneoconjunctival transition zone known as the limbus (5). The most common location is the interpalpebral area involving the bulbar conjunctiva and cornea. Lesions involving only the cornea or conjunctiva are less common and may indicate an aggressive clinical course (1, 4). Macroscopically, lesions can be leukoplakic, gelatinous, papilliform, or nodular. Occasionally, these may coexist (1, 2, 4).

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Most cases of OSSN present with redness, a foreign body sensation, and irritation in the eye; impaired vision on presentation is less common (1, 2). Patients can report a lump on the eye, causing them discomfort and pain. Examination of the lump may exhibit an elevated or flat, characteristic, and the lesion can be discolored from pearly gray to reddish gray, depending on the vascularity of the tumor (1, 2, 4).

Ocular squamous cell neoplasia can be diagnosed accurately based on its clinical features. Imaging methods like anterior segment optical coherence tomography in cases where medical treatment is preferred over surgical excision (7). The degree of involvement of dysplastic epithelium can determine the classification of preinvasive OSSN lesions as mild (CIN grade 1), moderate (CIN grade 2), and severe (CIN grade 3). Invasive OSSN is characterized by a breach of the basal epithelial basement membrane and invasion of the substantia propria (1, 3, 4).

Surgical excision with the "no-touch" technique and additional cryotherapy have been the mainstays of the initial treatment for OSSN (8). However, extensive surgical excision can lead to limbal stem cell deficiency, and excessive cryotherapy can cause iritis, ocular hypotony, and corneal hemorrhage (5, 8). These adverse effects paved the way for alternative pharmacological therapies. The three most effective compounds utilized as neoadjuvants and adjuvants include mitomycin C (MMC), 5-fluorouracil (5-FU), and interferon alpha-2b (IFN-α2b) (8). Although a combination of excision and topical treatment is often very effective, there are many adverse effects associated with these antimetabolites. The main complication of 5-FU is transient conjunctival hyperemia (4, 8). The major adverse effects of topical MMC are pain and corneal epitheliopathy. Its prolonged use can damage the ocular surface, cause allergic reactions and punctal stenosis (3, 4, 8). 5-FU can also cause corneal toxicity, but studies report the pain is not as severe as MMC (9). Complications of both 5-FU and MMC can be alleviated to a certain degree by using concurrent topical steroids and lubricating drops (8).

IFN-α2b is an immunomodulator with antiviral and antineoplastic properties. It can be administered topically or subconjunctivally. Compared to other antimetabolite agents, IFN-α2b is well-tolerated and does not cause ocular surface irritation (4, 8). However, subconjunctival delivery of IFN-α2b can cause systemic adverse effects such as myalgia and fever. As another disadvantage, treatment duration with IFN-α2b is longer than other treatment options for OSSN (4).

Another point to consider on immunomodulator drugs is the cost. 5-FU is notably affordable at 37 US dollars (USD) per cycle, with side effects that are generally manageable. On the other hand, IFN-α2b comes with a higher price tag in the US at 500 USD per month with a 95% success rate. MMC, costs roughly 300 USD per bottle (8). One drawback of topical IFN-α2b is the need for refrigeration, coupled with high compounding costs (approximately 600 USD for a month's supply in the US), though it can be much cheaper in Türkiye since in the US, patients typically bear the cost for compounded medications (10).

As a general approach surgical excision of OSSN with or without an additional cryotherapy process is still commonly performed; additionally, topical chemotherapy or immunotherapy are other popular monotherapy options (2-4, 8).

CASE REPORT

An 81-year-old male patient presented to the outpatient clinic with redness, increased lacrimation, and pain in his left eye for the past 3 months and was referred to Trakya University Hospital with a lesional finding on his left eye in the corneoscleral, limbal region (Figure 1). His physical exam showed ocular hyperemia, epiphora, and discomfort in his left eye. Biomicroscopic examination revealed corneoscleral invasion of the lesion approximately at the 5-7 o'clock position in his left eye, a large feeding vessel through the lesion, and conjunctival hyperemia (Figure 2). The patient showed no lymphadenopathy. Intraocular pressure was 13 mmHg in his right eye and 12 mmHg in his left, and fundus examination was normal in both eyes.

An excisional biopsy was performed. The pathology report described prominent atypical epithelium and stated a strong likelihood of invasive carcinoma at the lower limbus 5-7

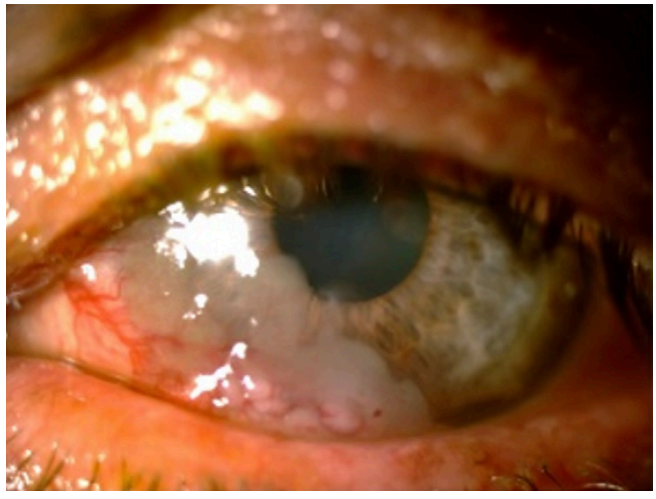

Figure 1: Left eye on presentation to clinic, corneoscleral lesion on limbus.

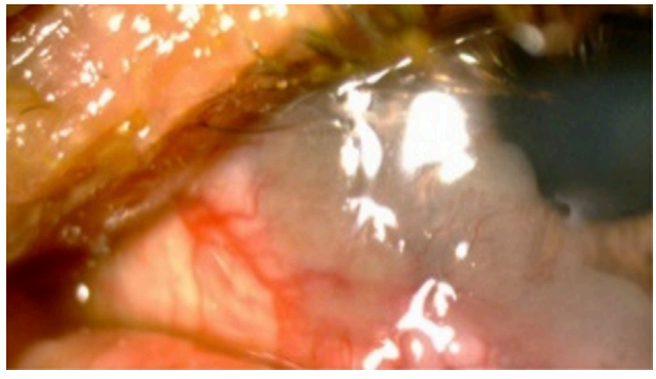

Figure 2: Large feeding vessel through the lesion, and conjunctival hyperemia.

o'clock position (Figure 3). In immunohistochemical staining, the surface epithelium was positive for Ki-67, p63, S-100, and CK-5 markers, revealing that the tumor is an invasive SCC, compatible with the patient's clinical picture.

During surgery under local anesthesia, the "no-touch" technique was performed, which allows the excision of lesions without any contact with the malignant tissue. This method is the most accepted modality for localized lesions to avoid the potential risk of seeding (11).

The management of OSSN involves alcohol-assisted de-epithelization of the lesion in the surgical bed, along with cryotherapy to the conjunctival margins. The patient underwent cryotherapy using the double-freeze thaw method. Following this, alcohol keratoepitheliectomy was performed to remove corneal components; scleral invasion was addressed with lamellar sclerectomy. Surgical margins were confirmed to be tumor-free in the pathology specimen, post-operatively. Additionally, a cryopreserved amniotic membrane was used to cover the resulting defect and reduce inflammation and fibrosis. The patient was discharged the same day after the operation. Moxifloxacin (w/v 0.5% eye drops, solution), dexamethasone (0.1% eye drops, suspension), and carboxymethylcellulose sodium (0.5% artificial tear drops) were prescribed four times per day for one week. IFN-α2b complements surgical excision for SCC, effectively targeting residual neoplastic cells to minimize recurrence risk and improve long-term outcomes (6). Therefore, the patient was administered topical IFN-α2b drops (1 million units/mL) four times a day for six months and followed up in the outpatient clinic every month. The medication is generally administered four times a day continuously, extending for one to two months after the lesion has clinically resolved. On average, clinical resolution takes approximately four months, which provided our rationale for using IFN-α2b for 6 months (9).

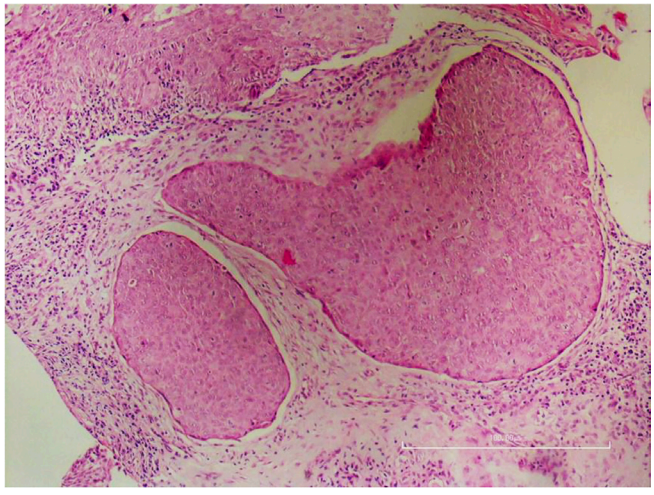

Figure 3: Excisional biopsy specimen, atypical epithelium at lower limbus 5-7 o'clock position.

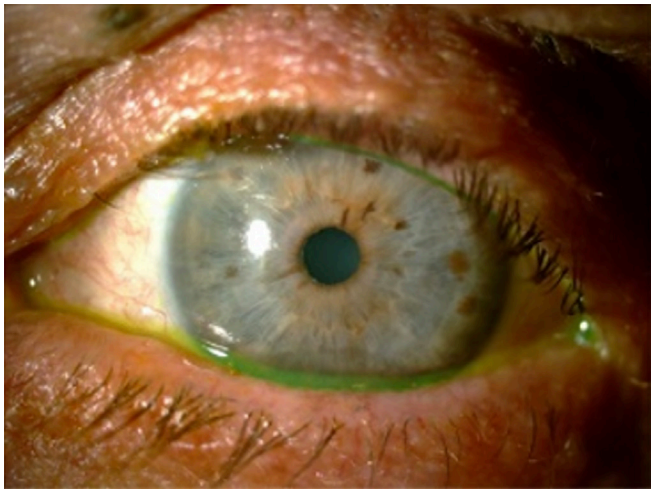

Figure 4: Left eye on the fifth year of follow-up.

The patient remained free of any topical or systemic side effects throughout the duration of the treatment. After using IFN-α2b for 6 months in the postoperative period, the lesion demonstrated total remission and no recurrence in five years of follow-up (Figure 4).

DISCUSSION

SCC is a variant on the OSSN spectrum, ranging from mild dysplasia to invasive carcinoma. Most frequently, it arises from the limbus, where malignant cells penetrate the basement membrane and invade the conjunctival subepithelium (3). Pai et al. (8) reported an SCC case arising from the palpebral conjunctiva as a rare presentation.

Ocular squamous cell neoplasia is a multifactorial pathology: advanced age, male gender, UV radiation exposure, viruses like HPV type 16, and HIV are some of the causes. As a key disease mechanism, UV radiation's mutagenic nature on the p53 tumor suppressor gene has been reported (2). OSSN is also associated with smoking, pale skin and iris color, immunosuppression, and vitamin A deficiency (2, 3).

Studies also suggest exposure to chemicals such as trifluridine, beryllium, petroleum products, and arsenic as other possible risk factors for OSSN (1, 3). Additionally, Hayashi et al. (12) reported a case of SCC caused by the long-term usage of an ocular prosthesis that originated from the upper palpebral conjunctiva. Our patient is known to use inhaled budesonide as an immunosuppressant drug due to chronic obstructive pulmonary disease. Therefore, this could serve as a predisposing factor for the development of SCC, besides the age and gender of our patient.

The clinical findings of OSSN can include ocular mass, pain, and redness, as well as vision loss and increased lacrimation. Lesions can be described in five different forms as gelatinous, papilliform, leukoplakic, nodular, or diffuse (2). Necrotizing scleritis has also been reported as an uncommon manifestation in some cases (13, 14).

Immunohistochemical markers such as MIB-1 (Ki-67), p16, p53, and p63 provide prognostic details about conjunctival SCC (12). We found that MIB-1 and p63 were positive in the patient's pathological specimen.

OSSN may be treated with chemotherapeutic agents like MMC and 5-FU or immunotherapeutic agents like IFN-α2b as well as surgical interventions. These agents exert their effects through distinct mechanisms, inhibiting tumor proliferation and facilitating resolution. MMC, through its action of cross-linking DNA strands, disrupts DNA synthesis, while 5-FU impedes thymidylate synthase, hindering DNA synthesis. In contrast, IFN-α2b modulates the immune response, augmenting anti-tumor activity. Clinical studies have demonstrated the efficacy of all three agents in treating ocular surface neoplasias, with resolution rates ranging from 75% to 100% for MMC, approximately 85% for 5-FU, and about 76-100% for IFN-α2b (9). While not as painful as MMC, 5-FU is associated with significant corneal toxicity. Although MMC may entail higher expenses and potential side effects like punctal stenosis, 5-FU presents as a relatively economical option. Notably, IFN-α2b eye drops generally exhibit minimal to no side effects (6, 9). Nevertheless, despite its effectiveness, MMC presents a significant burden of side effects. Therefore, if feasible, it is recommended to consider IFN-α2b or 5-FU as preferred treatment modalities (9). Topical chemotherapeutics can serve as neoadjuvants to reduce lesion size prior to surgery, offering the potential advantage of minimizing the excision area and thereby helping to prevent limbal stem cell deficiency (8). Additionally, anti-vascular endothelial growth factor agents have shown promise in the treatment of OSSN, both as primary therapy and as adjuncts to surgical excision (9). Özcan et al. (15) conducted the first study on the use of topical bevacizumab in the management of conjunctival neoplasms.

Adjuvant and neoadjuvant therapies serve to mitigate the risk of recurrence (6, 9). Microscopic subclinical residual disease is believed to contribute to recurrence rates, ranging from 33% with negative surgical margins to as high as 56% when margins are positive (6). Furthermore, Lee and Hirst (1) indicated that SCC has a higher recurrence rate than the milder grades of OSSN. Here, we demonstrated that despite the possibility of recurrence, our patient showed no recurrence through 5 years of follow-up after no-touch surgery and IFN-α2b treatment.

Footnote

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: H.G., Concept: H.G., Design: S.E., Y.H.E., İ.K., H.G., Data Collection and/or Processing: S.E., Y.H.E., İ.K., H.G., Analysis and/or Interpretation: S.E., Y.H.E., İ.K., H.G., Literature Search: S.E., Y.H.E., İ.K., H.G., Writing: S.E., Y.H.E., İ.K., H.G.*

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