Case report

Topical interferon alpha-2b eye-drops for treatment in a case of ocular surface squamous neoplasia

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Uso de interferón alfa-2b tópico como tratamiento en un caso de neoplasia escamosa de superficie ocular

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Abstract
Case presentation. An 80-year-old man with a history of squamous cell carcinoma of the ocular surface in the left eye, surgically resected ten years ago and in remission. He reports a mass growing on the ocular surface of that eye following blunt ocular trauma, associated with mild ocular pain, epiphora, and progressive decreased visual acuity. On examination, a conjunctival-corneal neoplasm was identified with 100 % corneal involvement. **Treatment.** Neoadjuvant treatment was initiated with topical interferon alpha-2b 1M IU/mL four times daily, which produced an immunosuppressive effect. The computed tomography scan of the orbits and brain revealed areas of calcification in the inferior temporal region of the left eye, with no evidence of tumor extension to adjacent tissues. Optical coherence tomography showed no tumor extension to the posterior pole. An excisional biopsy was performed using a "no-touch" technique, followed by treatment with interferon alpha-2b 1M IU/mL as adjuvant therapy. One year later, cataract surgery with intraocular lens implantation was performed. The final best corrected visual acuity in the left eye was 20/100 (logMAR 0.70). **Outcome.**The patient had a favorable clinical outcome, with no evidence of residual disease on clinical examination or optical coherence tomography of the left eye. The patient continued to undergo oncological follow-up for six months without recurrence.

Keywords
Eye Neoplasms; Carcinoma, Squamous Cell; Chemotherapy; Neoadjuvant Therapy; Chemotherapy, Adjuvant.

Resumen
Presentación del caso. Hombre de 80 años con antecedente de neoplasia escamosa de superficie ocular en ojo izquierdo, hace diez años resecada quirúrgicamente, en remisión. Refiere crecimiento de masa sobre superficie ocular en dicho ojo posterior a trauma ocular cerrado contuso, asociado a leve dolor ocular, epífora y disminución progresiva de agudeza visual. En la evaluación se identifica una neoplasia conjuntivo-corneal con compromiso corneal del 100 %. **Intervención terapéutica.** Se inició tratamiento neoadyuvante con interferón alfa-2b 1M UI/ml tópico cuatro veces al día que presentó un efecto inmuno-reductor. La tomografía computarizada de órbitas y cerebro reportó áreas de calcificación temporal inferior en el ojo izquierdo, sin evidencia de extensión tumoral a tejidos anexos. Ultrasonografía óptica no mostró extensión tumoral a polo posterior. Se realiza una biopsia excisional, con técnica «no touch» y posterior tratamiento con interferón alfa-2b 1M UI/ml como terapia de adyuvancia. Un año después se realiza cirugía de catarata más colocación de lente intraocular. La agudeza visual mejor corregida final en el ojo izquierdo fue de 20/100 (logMAR 0,70). **Evolución clínica.** Presentó una evolución clínica favorable, sin evidencia de enfermedad residual por evaluación clínica ni por tomografía de coherencia óptica en ojo izquierdo. El paciente continuó con vigilancia oncológica por seis meses sin recurrencia.

Palabras clave
Neoplasias del Ojo, Carcinoma de Células Escamosas, Quimioterapia, Terapia de Neoadyuvante, Quimioterapia Adyuvante.

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common neoplastic disease of the ocular surface and encompasses a spectrum of conditions affecting the corneal or conjunctival epithelium.[1-3] It was first described by Von Graefe in 1860;[4] the term was coined in 1995.[4] It is a disease associated with significant ocular and systemic morbidity and includes conjunctival intraepithelial neoplasia (CIN), corneal epithelial dysplasia, squamous cell carcinoma, and mucoepidermoid carcinoma;[5] it involves varying degrees of the epithelium or the entire epithelial thickness (carcinoma *in situ*), which can be a preinvasive or invasive lesion if it extends beyond the basement membrane with stromal involvement.[5-8] Invasive carcinoma usually manifests five to nine years after the onset of carcinoma *in situ*.[4]

The prevalence of squamous cell carcinoma varies by geographic region, ranging from 0.13 to 1.9 per 100 000; it accounts for 4 % to 29 % of orbital tumors and is the third most common type of ocular tumor, after melanoma and lymphoma.[4,9] It occurs predominantly in men over the age of 55.4 It is more common in Caucasians (90 % -100 %) and in regions at latitudes less than 30° from the equator.[4] The risk of recurrence and metastasis for this condition ranges from 5 % to 53 %, with a reported mortality rate of 8 % to 16 %.[10] It has a multifactorial etiology, including exposure to ultraviolet B radiation (UVB),9 human papillomavirus (serotypes 16 and 18 in intraepithelial neoplasia, six and 11 in conjunctival papilloma),[9,11,12] human immunodeficiency virus (HIV),[9,13] hepatitis B and C viruses. Predisposing factors include chronic smoking,[14] exposure to hydrocarbons, ocular and follicular hypopigmentation, xerophthalmia (vitamin A deficiency), exposure to chemicals such as arsenic and beryllium, and ocular trauma.[15-18] Failure of the DNA repair mechanism is evident in xeroderma pigmentosum and in exposure to ultraviolet B radiation, which induces mutations in the p53 gene in patients with ocular surface squamous cell carcinoma.[9,10,12,19]

Timely diagnosis of squamous cell carcinoma of the ocular surface is important for prognosis and therapeutic management.[3,7,20] Clinical presentation includes ocular irritation, a foreign body sensation, hyperemia of the bulbar conjunctiva, pruritus, and decreased visual acuity due to induced astigmatism or involvement of the visual axis.[9,17] It may present as an elevated lesion involving the cornea and bulbar conjunctiva, which macroscopically can be described based on its morphology as leukoplastic, gelatinous, papillary, nodular, or diffuse with characteristic feeding vessels.[5,7,9,17] Auxiliary diagnostic tools that have been described include cytology,[8,13] lesion staining,[13] and corneal optical coherence tomography (OCT) and anter (OCT).[13,21] According to the American Joint Committee on Cancer (AJCC), staging is based on tumor size and is classified into five categories, ranging from stage Tis (carcinoma *in situ*) to T4 with invasion of the orbit and adjacent structures.[22] Squamous cell neoplasms of the ocular surface are low-grade malignancies and rarely metastasize; however, they carry a recurrence risk of 5 % to 53 %.[10,22]

Treatment options are varied and tailored to the individual, with chemotherapy and surgery being the most impo rtant.[2,3,7,9,20,23,24] Surgical excision is the treatment of choice for lesions measuring four o'clock or less relative to the limbus, or with a basal diameter of 15 mm or less.[9,23,24] The "no-touch" technique described in 1997 by Shields *et al.*, with 3 mm to 4 mm clear margins, is the most recommended,[3,25,26] as is the use of cryotherapy.[6,27] Recurrence rates in the first two years following the "no-touch" surgical excision technique have been reported to range from 33 % with negative margins to 56 % with positive margins.[1,5] This highlights the importance of chemotherapy, both neoadjuvant and adjuvant, as a therapeutic adjunct to the surgical approach.[20,23,28] The use of drugs such as mitomycin C, 5-fluorouracil, and interferon alfa-2b (IFN) has been described as therapeutic options for noninvasive treatment of the ocular surface, achieving an effective therapeutic concentration with minimal adverse effects based on dose-response relationships.[3,9,14,20,23,28-31]

Interferon alfa-2b is a glycoprotein produced by leukocytes to combat viral infections. It possesses antiviral, antimicrobial, and antineoplastic effects, the latter resulting from a combination of antiproliferative, antiangiogenic, and cytotoxic effects.[13,29,32] It acts through direct and indirect mechanisms, with a cytostatic effect that prolongs the cell cycle in malignant cells and slows tumor growth by reducing access to metabolites. IFN inhibits enzyme biosynthesis, stimulates apoptosis, and induces the production of antibodies against tumor cells.[13]

Therapeutic use can be topical or perilesional as neoadjuvant therapy (immunoreduction), adjuvant therapy (immunoprevention), or as primary therapy (immunotherapy).[13,20,23,32-34] Adjuvant therapy with topical IFN has been shown to reduce the recurrence rate in patients with ocular surface neoplasms with positive margins.[9,26] IFN can be administered topically (most common), via ophthalmic eye drops, at a dose of one million IU/mL four times daily based on dose-response until one to three months after tumor resolution,[13,29,35] and perilesionally at a dose of three million IU/0.5 mL weekly until resolution.[13]

It has fewer adverse effects and is better tolerated compared to mitomycin C and 5-fluorouracil.[9,13] Mild adverse effects include follicular conjunctivitis, keratitis, corneal ulcer, epithelial microcysts, and flu-like symptoms (occurring in 33 % of cases with perilesional administration).[13,23]

Other treatments have been described, such as radiation therapy, photodynamic therapy, anti-angiogenic agents, cidofovir, and epidermal growth factor receptor inhibitors.[13,36]

It is important to consider the side effects and complications of medical and surgical treatment.[37,38] Medical complications to consider include drug toxicity, keratitis, scleral thinning, and sclero-keratitis.[28] Likewise, surgical complications may include tumor recurrence, scleral thinning and/or necrosis, corneal thinning, and/or corneal perforation.[38] The differential diagnoses for squamous cell carcinoma of the ocular surface include actinic keratosis, benign intraepithelial dyskeratosis, conjunctival or tarsal cysts, conjunctival hemangioma, keratoacanthoma, malignant melanoma, pannus, pinguecula, pterygium, pseudoepitheliomatous hyperplasia, pyogenic granuloma, and xerophthalmia.[4]

Case presentation

An 80-year-old male patient who had undergone resection of a squamous neoplasm of the ocular surface in his left eye ten years prior and was in remission presented with a five-month history of mass growth in his left eye following blunt ocular trauma. He reported mild ocular pain, a foreign body sensation, epiphora, and progressive decreased visual acuity in that eye. In addition, he reported having been a farmer for many years, a surgical history of cataract surgery in the right eye five years ago, and a medical history of long-standing systemic hypertension treated with 150 mg of irbesartan daily and benign prostatic hyperplasia treated with 5 mg of terazosin daily. He denied smoking, alcohol abuse, allergies, or other medical history.

On examination, he had a best-corrected visual acuity of 20/100 (logMAR 0.70) in the right eye and finger counting at two feet (logMAR 2) in the left eye. Under the slit lamp, intraocular pressure was measured at 14 mmHg in the right eye, and the left eye had a normal tonodigit reading. A raised conjunctival-corneal neoplasm was identified in the left eye, with diffuse borders, a mottled appearance, 100 % involvement of the corneal epithelium, and the presence of 360° peripheral neovessels, as well as diffuse moderate conjunctival hyperemia (Figure 1A). No preauricular, retroauricular, or cervical lymphadenopathy was palpable. was diagnosed as a suspected recurrent squamous cell carcinoma of the ocular surface in the left eye.

Treatment

Neoadjuvant treatment was initiated with interferon alfa-2b 1M IU/mL at a dose of one drop four times daily, along with topical ocular lubricants in the left eye. Ophthalmological studies were ordered, including left-eye corneal optical coherence tomography (OCT) and optical ultrasonography, as well as computed tomography (CT) scans of the orbits and brain.

The ordered laboratory tests, complete blood count and blood chemistry, were reported within normal ranges. Rapid serological tests for HIV, VDRL, and antibodies against hepatitis B and C were negative. At the four-week follow-up, the patient had a best-corrected visual acuity of 20/400 (logMAR 1.30) in the left eye. Furthermore, slit-lamp examination of the left eye revealed a reduction in tumor burden predominantly in the temporal region, involving the nasal 50 % of the cornea (Figure 1B). Computed tomography of the orbits and brain showed areas of inferior temporal calcification in the left eye, with no evidence of tumor extension to adjacent tissues (Figure 2). Corneal optical coherence tomography of the left eye revealed hyperreflectivity and a corneal thickness of 1630 microns with epithelial involvement (Figure 3), and optical coherence tomography of the same eye revealed posterior vitreous detachment without tumor extension to the posterior pole.

The same topical treatment was continued, and the patient was reevaluated four weeks later. However, at the next follow-up visit, a reduction in tumor burden was observed, predominantly in the superior and temporal regions, with 40 % of the nasal cornea involved (Figure 1C). Consequently, it was decided to perform a surgical approach, excisional biopsy of the conjunctival- corneal neoplasm, in that eye using a "no-touch" technique.

At the immediate postoperative follow-up, adequate healing of the conjunctival tissue was observed. At the one-week postoperative follow-up, the left eye was evaluated using a slit lamp; the cornea showed mild diffuse opacity, good corneal and conjunctival re-epithelialization, and few inferior limbal vessels; therefore, a follow-up corneal optical coherence tomography (OCT) scan of the left eye was indicated, which reported a corneal thickness of 423 microns, with no evidence of lesion or epithelial involvement (Figure 4A). The biopsy revealed an invasive, well-differentiated, keratinizing squamous cell carcinoma with positive surgical margins (Figure 5); therefore, adjuvant treatment with interferon alfa-2b 1M IU/mL was initiated at a dose of one drop four times daily for four weeks in the left eye. At the one-month and six-month postoperative follow-ups, no signs of residual disease were

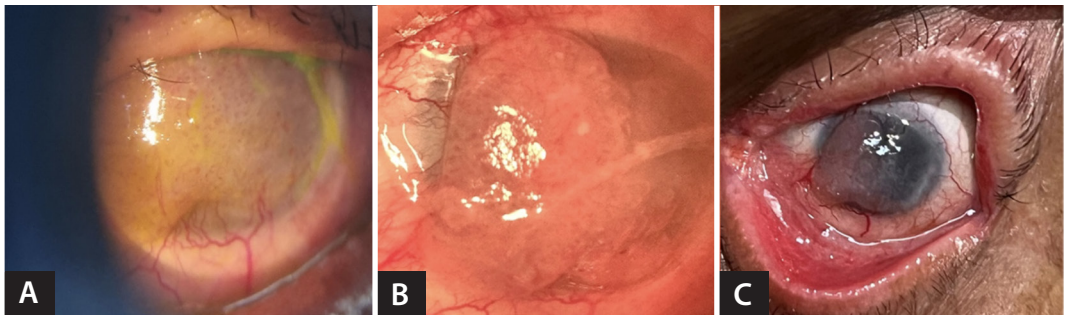

Figure 1. Clinical course of the left eye during treatment. A) Initial slit-lamp examination. There is evidence of 100 % involvement of the corneal epithelium and the presence of 360° peripheral neovessels with inferior feeding vessels. B) Evaluation of the same eye 4 weeks post-treatment, showing evident cytoreduction of the tumor burden on the corneal surface. C) Follow-up at 8 weeks after the start of treatment, showing a reduction in tumor size, with superior and temporal involvement.

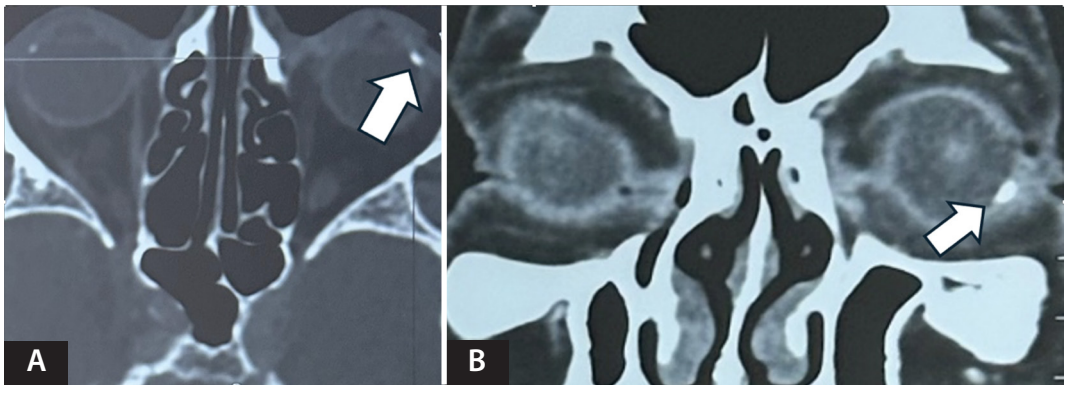

Figure 2. Computed tomography of the orbits and brain showing inferior temporal calcification in both views. A) Bone view in the axial section. B) Soft-tissue view in the coronal section.

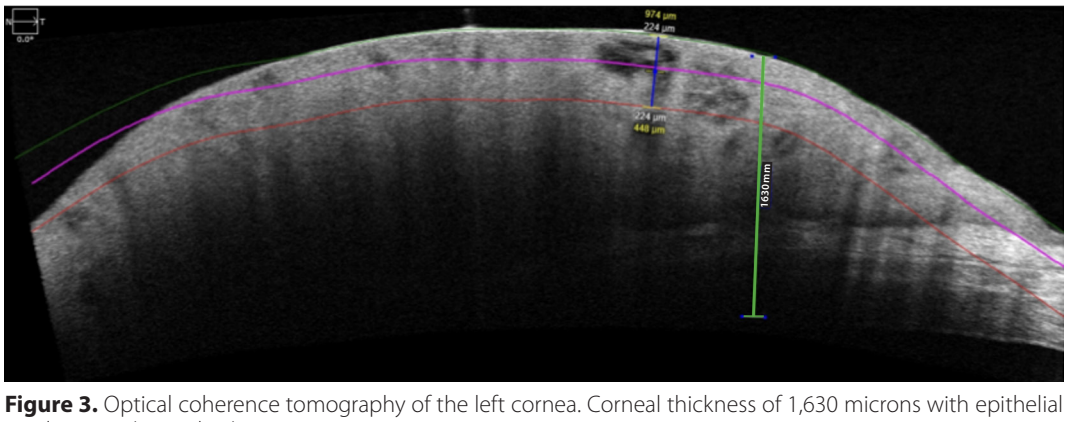

Figure 3. Optical coherence tomography of the left cornea. Corneal thickness of 1,630 microns with epithelial involvement (green line).

evident in the left eye (Figure 4B); therefore, the patient remained under oncological surveillance and was monitored to evaluate the need for cataract surgery in that eye. One year after the initial surgery, cataract surgery was performed via phacoemulsification of the lens and implantation of an intraocular lens, without complications. Postoperative best-corrected visual acuity in the left eye was 20/100 (logMAR 0.70); the patient is currently being followed up for six months for oncological surveillance with no evidence of tumor growth.

Clinical evolution

The patient had a satisfactory clinical course, with no evidence of residual disease either on clinical evaluation or on imaging studies (corneal optical coherence tomography), which showed a decrease in corneal thickness from 1630 to 423 microns in the left eye. The patient remained under oncological surveillance for one year following initial treatment and for six months following cataract surgery. Additionally, an improvement in visual acuity was observed, with satisfactory results.

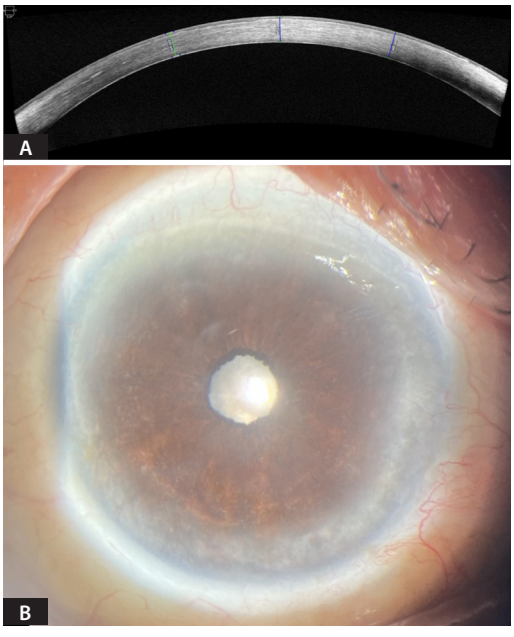

Figure 4. A) Follow-up corneal optical coherence tomography of the left eye. Corneal thickness of 423 microns. B) Six-month postoperative slit-lamp examination of the left eye.

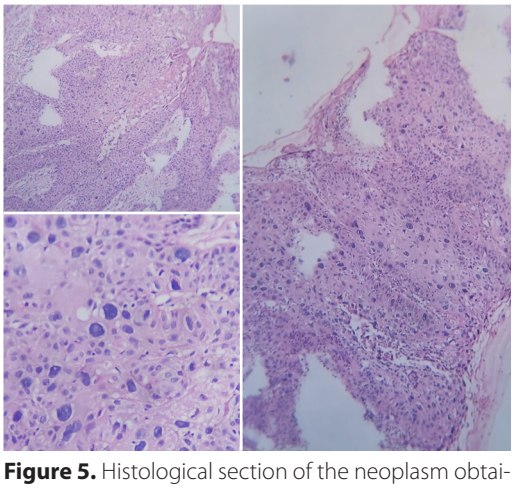

Figure 5. Histological section of the neoplasm obtained by biopsy. A well-differentiated, invasive malignant squamous cell carcinoma is identified, consisting of medium- to large-sized cells with marked nuclear atypia, abundant eosinophilic cytoplasm, intercellular bridges, and focal intracellular keratinization.

Clinical diagnosis

Recurrent T2 ocular surface squamous cell carcinoma was diagnosed in the left eye.

Discussion

Squamous cell carcinoma of the ocular surface is a condition that can involve the cornea, the conjunctiva, or both;[1-3] the latter was the presentation described in this case. The clinical presentation was that of a locally recurrent neoplasm following ocular trauma, which constitutes an associated risk factor, since, during the remission period, it can stimulate the proliferation of latent cells and lead to progressive growth.[16-19] Recurrences have been reported in up to one-third of patients within the first ten years following surgical treatment.[18,19] Timely clinical diagnosis was essential for combined treatment,[3,6,8,10,18,21] which had a positive impact on the patient's prognosis. Although the neoplasm involved the entire cornea, neither computed tomography nor ocular ultrasonography revealed invasion of adjacent structures or within the eyeball; therefore, it was classified as a T2 ocular surface squamous cell carcinoma. The use of chemotherapy with interferon alfa-2b proved effective as neoadjuvant therapy for immune- reduction,[13,14,20,21,23,24,32-36] with a 73.62 % reduction in tumor size objectively demonstrated by corneal optical coherence tomography. In addition, the tumor was found to extend across approximately 40 % of the corneal surface prior to surgical intervention. Furthermore, the imaging studies performed allowed for staging, which influenced the diagnosis and treatment.[14,22,23] Interferon alfa-2b was the chemotherapeutic agent of choice for neoadjuvant and adjuvant therapy over alternatives such as 5-fluorouracil due to its superior safety profile and higher efficacy rate (80 %-100 %). In the geriatric population, the ocular toxicity of 5-fluorouracil can compromise the integrity of the ocular surface and quality of life. Interferon alfa-2b, with its mild adverse effects and better local tolerance, allowed for optimal epithelial recovery. Although this clinical decision entails a higher cost, it is justified by the need to maximize adherence and minimize the risks of scleral necrosis or perforation in an eye with recurrent neoplasia and a history of prior surgery.[13,20,23,32-34] As described in other studies, adjuvant treatment, such as immunoprophylaxis with interferon alfa-2b, to prevent recurrence following surgical resection was equally effective, no recurrence was observed during oncological follow-up one year after the initial chemotherapy and surgery, and six months after cataract surgery.[10,21,23-25,29] Therefore, It was established that oncological follow-up is essential for identifying treatment-related recurrences.[4,37,38] It is important to note that clinical characteristics, corneal optical coherence tomography, histopathological history, and identified risk factors made it possible to establish a definitive diagnosis among differential diagnoses such as pterygium, pannus, actinic keratosis, pyogenic granuloma, dyskeratosis, and others.[4]

Ethical Considerations

The 2013 Declaration of Helsinki was followed, and the confidentiality of the patient's personal and identifying information was ensured. Additionally, the patient's authorization for the presentation of the clinical case was obtained through written informed consent.

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