Short communication

Interferon alpha 2β, partial keratectomy and amniotic membrane transplant for the treatment of a recurrent conjunctival squamous carcinoma

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ARTICLE INFO

Article history:
Received 4 June 2010
Accepted 28 January 2011
Available online 14 October 2011

Keywords:
Squamous carcinoma
Conjunctiva
Eyelid
Keratectomy
Interferon alpha 2β
Amniotic membrane

ABSTRACT

Case report: An 80-year-old woman diagnosed with a recurrent squamous conjunctival carcinoma treated with surgical excision of the lesion, zonal reconstruction and topical interferon alpha 2β.

Discussion: Squamous conjunctival carcinoma is the most frequent neoplasm of the ocular surface. Surgical removal of the lesion is the traditional treatment, but this technique has a high recurrence rate. Interferons are glycoproteins that trigger intracellular pathways with antiviral and antitumoral properties. Recent studies have proven their activity against conjunctival carcinoma.

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Interferón alfa 2-β, queratectomía parcial y trasplante de membrana amniótica para el tratamiento de un carcinoma escamoso conjuntival recidivante

RESUMEN

Caso clínico: Mujer de 80 años de edad diagnosticada de carcinoma escamoso conjuntival recidivante tratado con escisión quirúrgica de la lesión, reconstrucción zonal e interferón alfa 2β tópico.

Discusión: La neoplasia escamosa de la conjuntiva y córnea es el tumor más frecuente de la superficie ocular. La cirugía mediante resección de la lesión es el método tradicional de tratamiento de estos tumores, pero presenta un elevado índice de recurrencias. La inmunoterapia es una alternativa actual para estos tumores. Los interferones son...
Clinical case

An 80-year-old woman was referred by another service due to conjunctival tumoration in the right eye (RE) dated 5 months back. Personal history of interest includes the removal of a small upper-external palpebral papilloma in the RE one year back. Corrected visual acuity in RE, measured with Snellen optotypes, was of 0.65 and in the left eye (LE) of 0.8.

The ophthalmological exploration carried out in the right eye revealed a conjunctival tumoration with the appearance of a papilloma in the internal edge, involving the half-moon fold and caruncle with dilated capillary crests and extension to the sclero-corneal limbus at approximately 3 o’clock. The lesion was more prominent in the lower area, slightly displacing the lower eyelid and causing a discrete ectropion of the middle third of the palpebral edge. The new tissue comprises the inferior and superior lacrimal points and extends toward the skin of the internal edge. An ulcerated cutaneous lesion is also observed in the upper eyelid with chronic inflammatory signs (Fig. 1).

The patient provided the anatomopathological report of the lesion biopsy which diagnosed squamous carcinoma. Nuclear magnetic resonance was performed to discard retro-ocular infiltration. Considering the diagnostic orientation of squamous carcinoma involving the superior and inferior eyelids and the nasal conjunctiva of the right eye, the patient underwent surgery to remove the lesion and reconstruct the involved area with a free conjunctiva graft obtained from the temporal quadrant placed over the middle rectum area and a muscle-skin pediculated graft to repair the internal edge. Biopsies were made of all the removed fragments, recommending follow-up by a general oncologist. The initial surgical and functional result is excellent and the anatomopathological report of the lesion confirms the squamous carcinoma diagnostic with resection margins free of the lesion at the palpebral level and infiltrating squamous carcinoma with a minimum damaged area which makes contact with the resection edge in the bulbar conjunctiva of the sclero-corneal limbus. Due to said location, it was decided to maintain an expectant attitude.

Fourteen months after the intervention, in a regular checkup a white-grayish lesion was observed, including vascularization and corneal infiltration between 12 and 6.30 o’clock in the nasal quadrant. A 3.8 mm geographic corneal epithelial defect was evidenced, with thinning, at 3 o’clock close to the limbus (Fig. 2). A diagnostic of relapsing conjunctival carcinoma was suspected, initiating treatment with interferon alpha 2b in a concentration of $1 \times 10^6$ UI/ml 5 times a day during 2 months. In this period, initially the epithelial defect was reduced and the relapse regressed. Considering the positive evolution, it was decided to continue the topical treatment, but 4 months later an extension of the lesion was observed over the cornea (Fig. 3). Due to the diagnostic impression of relapsing squamous carcinoma, the recurring lesion was surgically removed with a partial laminar half-moon keratectomy performed with 2 trephinitors having different diameters, resection of the entire bulbar conjunctiva and reconstruction of all the resected area with an amniotic membrane graft, fixed by means of continuous 10-0 nylon suture utilizing transfixating points and anchoring it to the superficial scleral layers to avoid early dislocation (Fig. 4). Five days after the intervention and after removing the occlusive...
bandage, topical treatment was resumed with interferon alpha 2b 5 times a day.

In the immediate postop, the amniotic membrane remained in position up to complete reabsorption without dislocation. This was attributed to the continuous suture with numerous anchoring points. After verifying the complete disappearance of the membrane, the suture was withdrawn. The nasal bulbar conjunctiva formed skin adequately and no signs of carcinoma relapse were observed during the follow-up period. Conjunctival impression cytology were performed to monitor the histological appearance of the corneal epithelial and superficial conjunctival cells due to the degree of invasion of the area caused by the lesion in its initial stages, even though its systematic execution is open to debate.

After a 9-month follow-up and the second surgery no visible relapse was observed, with a corrected visual acuity of 0.4 in the right eye. At present, the patient remains under treatment with interferon alpha 2b eye drops 5 times a day and artificial tears without exhibiting new suspect tumor lesions or local side effects caused by the medication.

**Discussion**

 Conjunctival squamous neoplasia is the most frequent tumor of the ocular surface. Initially, this lesion is confined inside the epithelium strata and is known as conjunctival intraepithelial neoplasia (CIN). There are 3 stages of CIN depending on where the lesion appears: in the external third (stage I CIN or slight dysplasia), the external thirds (stage II CIN or moderate dysplasia) or the thickness of the entire epithelium (stage III CIN or severe or in situ carcinoma). It appears as a slowly progressing unilateral lesion with low malignity potential. Predominantly, it expresses in elderly males. When the neoplastic cell growth goes through the baseline membrane it is known as invasive squamous carcinoma. Its etiology is not entirely clear and it could possibly be due to multiple factors. It could represent an abnormal maturation of the corneal and conjunctival epithelium as the combination of factors such as ultraviolet B radiation and human papilloma virus 16 and 18.

At the clinical level, these lesions are of variable shape and low height, clearly differentiated from surrounding normal tissue, usually accompanied by nutritional vascularization and its color ranges from pearl gray to grayish red. Its most frequent location is at the nasal limbus, possibly due to the greater exposure to UV radiation of the nasal area or, with less frequency, in the temporal conjunctival area in the interpalpebral fissure.

It is necessary to perform a histological diagnostic before beginning treatment, depending on the size of the lesion. In small lesions, a complete excisional biopsy thereof is the most frequently utilized technique. In large or extensive tumors, small focal biopsies can be carried out to determine the diagnostic and plan the most adequate surgical technique. An additional alternative of recent appearance consists in obtaining cytological samples either through impression or brushing for the diagnostic and postop monitoring period.

Simple surgery with a single resection of the lesion is the traditional method for treating these tumors even though it exhibits a high recurrence rate (25–53%) due to the difficulty in obtaining edges without infiltration. If the underlying corneal or scleral tissue is invaded, it could be necessary to perform lamellar keratoplasty and scleroplasty.

When carrying out broad resections, it is necessary to utilize tissue to rebuild the surgical resection surface. We can utilize rotational pediculated conjunctival flaps, free conjunctival flaps of the same eye or the contralateral one and, in large resections, it would be advisable to utilize amniotic membrane as in the present case. It is important to use a sophisticated suture technique if we utilize amniotic membrane to cover the treated area due to the significant tendency toward dislocation observed with this tissue. Our preference is for a continuous suture technique anchored in the sclera following the entire anterior, lateral and posterior edges of the implanted membrane. The size of the membrane is adjusted to the area in which the resection has been performed. Likewise, it is extremely important to utilize a sophisticated surgical technique following the non-touch technique proposed by Shields.
with the aim of avoiding the dispersion of tumor cells during surgery and the subsequent local relapses. According to this technique, the lesion must be resected starting from healthy tissue about 4 mm beyond the discernible edges of the lesion. The latter must not be touched or washed with any solution to avoid the dissemination of neoplastic cells which could take hold and give rise to a relapse. Bleeding scleral and conjunctival vessels must be carefully cauterized, withdrawing a fine layer of sclera at the base of the lesion. In addition, absolute alcohol must be applied with a sponge to induce necrosis and eliminate cells from the entire resection substrate. Subsequently, dual step cryocoagulation of all the conjunctival margins of the resection must be carried out.

Radiotherapy (strontium-90, β-therapy, and γ-therapy) is no longer used due to its frequent and dangerous complications, although it may be necessary for large lesions and always in association with other procedures. Relapses usually occur in the first 2 years after surgery.

Topical chemotherapy has been proposed for treating primary conjunctival tumors and after relapses, although the limited penetration of these agents can give rise to failures in the eradication of the tumor. The most widely utilized drugs are 5-fluorouracil and mitomycin C.3

Immunotherapy can be utilized as an alternative or as supplementary therapy for treating these lesions. Interferons are glycoproteins which activate a cascade of intracellular events which confer antiviral and antitumoral properties. Interferon alpha 2β can be applied topically as eye drops or injection in the lesion. Its administration has been described as the initial and isolated treatment for conjunctival intraepithelial neoplasia and as supplementary therapy to surgery of invasive squamous carcinomas, providing good results with low side effect rates.4,5 Boehm described topical interferon treatment in a series of 7 eyes with relapsed conjunctival and corneal intraepithelial neoplasia in a frequency of 4 times a day up to resolution, with a mean time up to elimination of the tumor of 14.5 weeks. The side effects of the topical application of interferon are usually slight and consist in conjunctival hyperemia and follicular conjunctivitis, which were not observed in our patient.

In the present clinical case, the utilization of interferon alpha 2β after the first relapse exhibited only temporary efficacy because even though in the first 2 months the lesion reduced its size and the corneal epithelial defect epithelialized, subsequently it increased in size. In the second relapse, immediately after surgery treatment was established with interferon alpha 2β and, after 9 months follow-up we have not observed a recurrence of the conjunctival carcinoma as described by some authors. In this case, considering the evolution and aggressiveness of the initial lesion and the absence of observed local side effects, it was decided to continue the long-term administration of the interferon eye drops to ensure the absence of relapse 9 months after the last surgery.

**Conflict of interests**

None of the authors have declared any conflict of interests.

**References**


