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Case Report

Exclusive Ru-106 brachytherapy for the management of a recurrent corneo: Conjunctival squamous cell carcinoma

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ABSTRACT

BACKGROUND: We report a case of personalized exclusive brachytherapy treatment for the management of a highly recurrent squamous cell conjunctival carcinoma with corneal invasion.
CASE DESCRIPTION: This is a case of a Caucasian 81-years-old man who presented 10 years ago to our clinic with a pink-white para-limbal mass with dilated feeder arteries and mild leukoplakia. Excisional biopsy confirmed the presence of conjunctival intraepithelial neoplasia (CIN). Successively, he underwent two 4-weeks cycles of Mytomicin C topical therapy and a second excisional surgery, due to several recurrences of the lesion. At the last relapse, the pink-white peri-limbic mass which invaded the corneal limbus, determining corneal opacification from 5- to 7-clock hours, was confirmed by anterior segment optical coherence tomography (AS-OCT). Due to resistance to MMC therapy and chronic epitheliopathy, an AS-OCT guided exclusive radiotherapy plan was set: a Rhutenium-106 CCD plaque was applied directly over the afflicted corneal surface, the corneal limbus and the neighboring sclera for 24 hours. The remission of both conjunctival and corneal malignancy was complete 2 months after surgery and no signs of recurrence were highlighted at AS-OCT analysis at the 2-year follow up.
CONCLUSION: Brachytherapy treatment showed optimal management of both corneal and conjunctival involvement, with a free-of-disease follow-up of 24-months. This result suggests that, in specific conditions, Ru-106 brachytherapy could be an effective option of treatment even if not associated with surgical excision.

Keywords: Anterior segment optical coherence tomography; Brachytherapy; Personalized medicine; Ru-106; Squamous cell conjunctival carcinoma

Introduction

The most common ocular surface cancer is squamous cell conjunctival carcinoma (SCCC) (1). Greater incidences are reported in elderly and tropical regions, where patients are more often exposed to high levels of ultraviolet light (2). Human papillomavirus (HPV) and human immunodeficiency virus (HIV) infections are additional risk factors (3,4).

Although the likelihood of distant (1–6%) and local (3–9%) metastases is very low in SCC patients (5,6), the tumor's natural location makes treatment challenging since treatment-related toxicity must be kept to a minimum (7).

Conjunctival SCC often affects the limbal area and may take on a variety of shapes, including sessile, papillomatous, or nodular appearances, sometimes exhibiting signs of leukoplakia and pigmentation.

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Depending on the location and size of the tumor, conjunctival SCC may be managed with excisional biopsy, alcohol-treated restricted superficial keratectomy, conjunctival cryotherapy using the no-touch approach, but also with topical medicines that include mitomycin C (MMC), 5-fluorouracil, and interferon alfa-2b (8–11). Surgery is generally the first therapy approach of these malignancies, with recommended minimum safety resection margins of 3 to 4 mm (2,12). Disease control with clean surgical excision margins for SCC has been reported to reach 100%; however, the recurrence rate with residual tumor cells in the wound margins may vary from 36% to 53%. In addition, adjuvant treatment such as topical chemotherapy, external beam radiation therapy (EBRT), or brachytherapy can be needed to reduce the incidence of local failure (13,14).

Very few studies report the outcomes of patients treated with brachytherapy so far, with recurrence rates ranging from 0% to 20% when used in adjuvant setting (15–19).

In this study, we report a case of exclusive brachytherapy treatment for the management of a highly recurrent SCC with corneal invasion.

Case presentation

This is a case of a Caucasian 81-years-old man who presented 10 years ago to our clinic. His visual acuity was 20/20 in both eyes, and he was bilaterally pseudophakic. In his left eye (LE), a slit-lamp examination showed a pink-white para-limbal mass with dilated feeder arteries and mild leukoplakia, but no corneal involvement. In the suspect of a conjunctival neoplasia, he underwent excisional biopsy and subsequent histological examination, highlighting the presence of a papillomatous proliferation with cytoarchitectural atypia, confined to the epithelium (conjunctival intraepithelial neoplasia, CIN). Owing to histological evidence of invasion of the excision margins, an adjuvant therapy with a four-weeks cycle

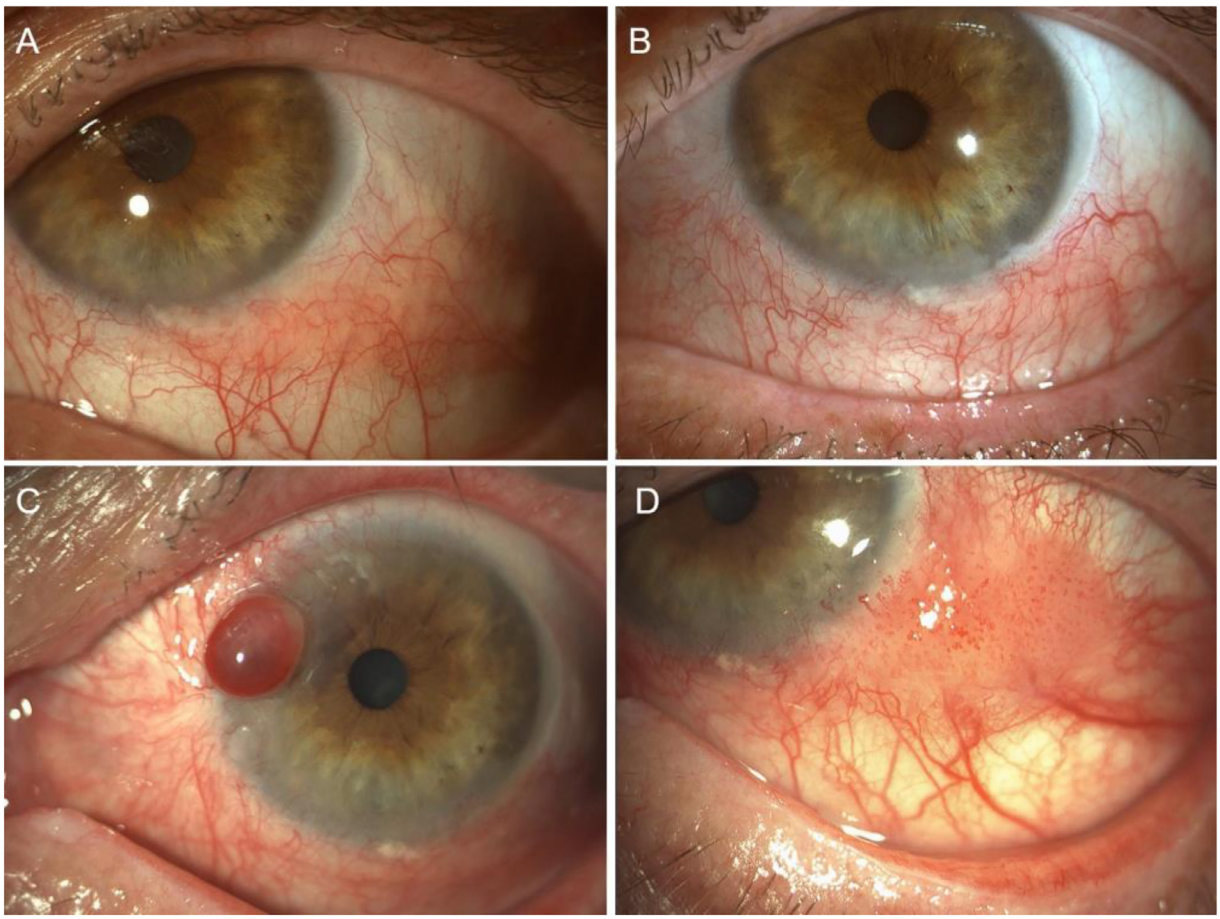

Fig. 1. Slit-lamp examination of several recurrences of this squamous cell conjunctival carcinoma. (a) At presentation, a pink-white para-limbal mass with dilated feeder arteries and mild leukoplakia is visible, but no corneal involvement, which was reported to be conjunctival intraepithelial neoplasia after histological examination; (b) One year after, a recurrence of the pathology in the same localization was reported, and the patient underwent a cycle of MMC; (c) Three years after, a paralimbic supero-nasal reddish gelatinous lesion, with small telangiectatic vessels, was found, and necessitated a novel MMC cycle with temporary benefit; (d) Finally, two years after, a novel recurrence of the neoplasia at the temporal bulbar conjunctiva, invading corneal limbus, was reported.

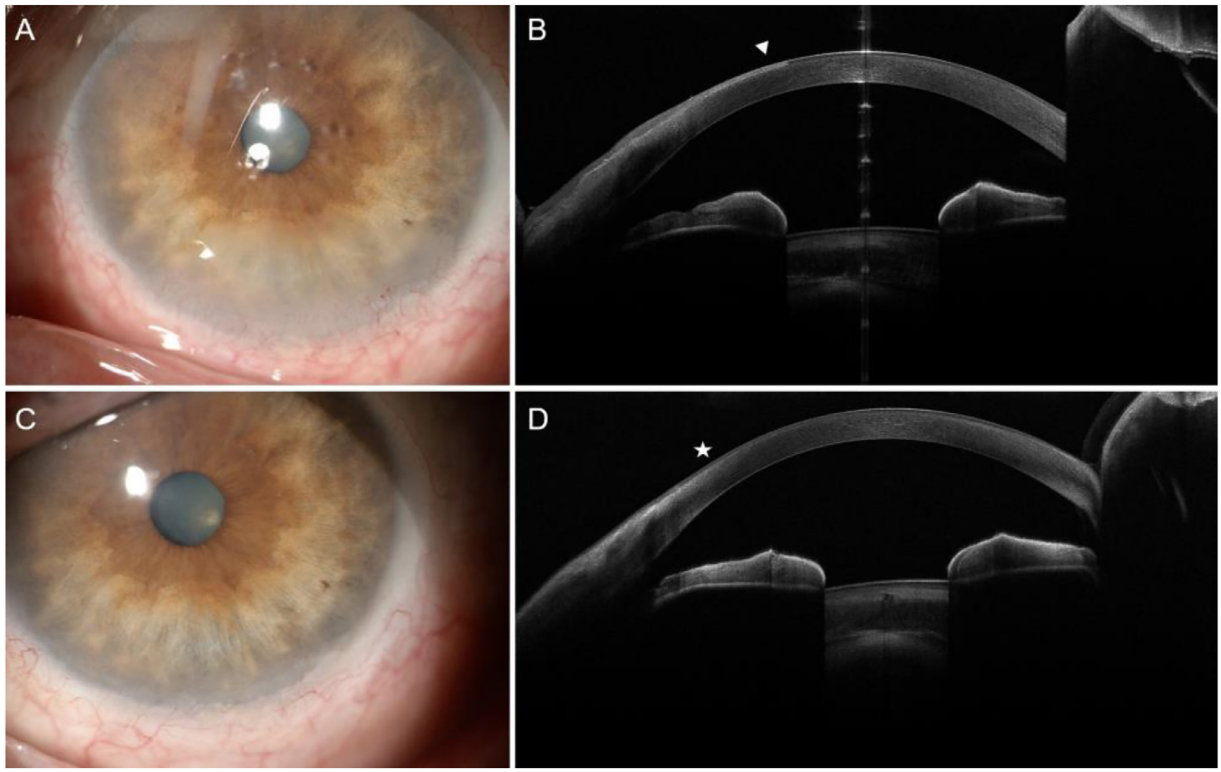

Fig. 2. Slit lamp examination (a) and anterior segment optical coherence tomography (AS-OCT) image (b) highlighting the limbus invasion in the inferior quadrant of the cornea, lapping the optical zone. After exclusive brachytherapy treatment, a complete regression of the pathology was reported and sustained over time, at the 24 months follow up, as visible at slit lamp examination (c), but also confirmed by AS-OCT scans (d).

of Mytomicin C 0.02% (MMC) topical therapy was set up and allowed for complete regression of the pathology. Following a year, there was a report of pathology recurrence in the same location. The patient received a second cycle of MMC, which showed clinical improvement and led to a lesion regression under close follow-up monitoring.

Unfortunately, three years after, the recurrence of a paralimbic supero-nasal reddish gelatinous lesion, with small telangiectatic vessels, was highlighted at the annual follow-up visit. For this reason, the patient underwent a third four-weeks cycle of MMC 0.02%, with initial clinical benefit and no adverse effect. Afterwards, he was scheduled for a six-monthly follow-up.

Nevertheless, two years after, he experienced a novel recurrence of the neoplasia at the temporal bulbar conjunctiva, invading corneal limbus (Fig. 1). A second excision surgery was performed, and histological examination confirmed the presence of a squamous conjunctival carcinoma with focal stromal microinvasion. Exeresis margins were free of disease. Additionally, he underwent five intravitreal injections of ranibizumab for his neovascular age-related macular degeneration (nAMD) in his LE, with unfavorable visual results.

The patient was free of relapse for the following two years. However, in the last months of 2020, the slit-lamp examination showed the presence of a gelatinous lesion involving the conjunctiva at the limbus and infiltrating the cornea from 5- to 7-clock hours as an opalescent epithelial lesion with irregular, scalloped borders. The presence of a solid tumor infiltrating the corneal epithelium was suggested by the anterior segment optical coherence tomography (AS-OCT), which showed epithelium hyperreflectivity that lapped the optical zone.

As first line of treatment, he underwent a four-weeks cycle of topical MMC 0.02%, which revealed ineffective and caused chronic corneal epitheliopathy. Due to the extent of the limbal and corneal invasion, the patient was scheduled for brachytherapy.

Prior to surgery, a radiotherapy plan was set up: the treatment site was measured with both UBM and AS-OCT to establish the depth of the procedure, which included all superficial structures that needed to be treated, most often the corneoscleral bed and the episcleral tissues, with a margin of 0.5 mm. Intraoperatively, a Rhutenium-106 CCD plaque was applied directly over the afflicted corneal surface, the corneal limbus and the neighboring sclera. As visible in the plaque simulator treatment plan (Fig. 3), the prescribed (Rx) dose was 100 Gy at the apex for the tumor, with an apex height of 1.00 mm and a base expansion margin of 2.00 mm. Plaque was positioned above the inferior hemi-cornea and the perilimbal conjunctiva.

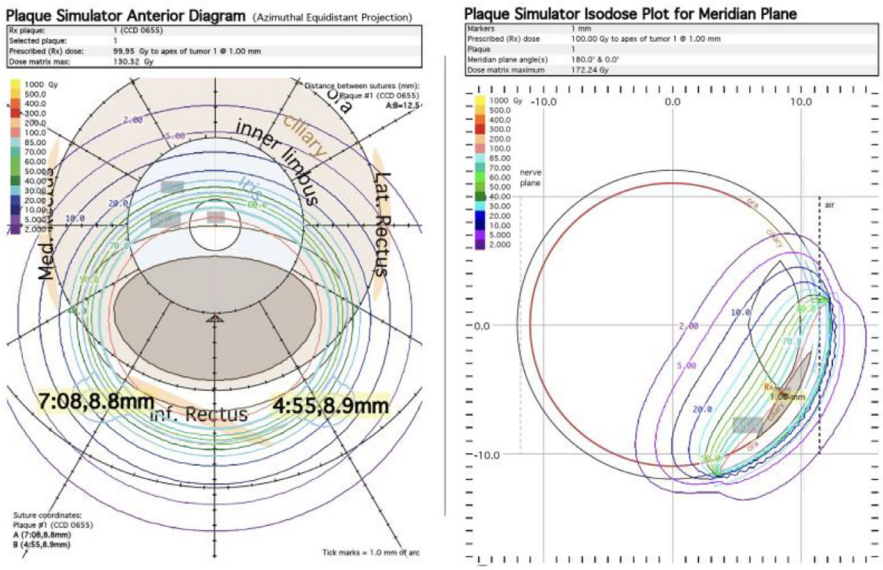

Fig. 3. Report of the plaque simulator treatment plan, in both frontal view (on the left) and lateral view (on the right). Colored lines define the maps of isodose, with the number above each line indicating the amount of absorbed radiation in the perilesional area. The internal red line corresponds to the tumor area, for which a 100 Gy dose was prescribed. Ocular structures are graphically represented and the name of each structure is clearly specified. Data regarding the plaque subtype (CCD 0655), prescribed (Rx) dose, markers and dose matrix maximum are highlighted in the two tables above the treatment plan. A color scale of Gy dose is visible in the upper left portion of the plans.

The plaque was kept in place for 24 hours and then removed. Epithelial erosion was observed just after treatment, resolving in 7 days thanks to supportive lacrimal substitutes and therapeutic LAC. We did not report any evidence of anterior chamber inflammation or other signs of early local toxicity.

Following treatment, a full remission of both conjunctival and corneal malignancy was reported with no signs of malignancy 2 months after surgery. After almost two years of follow-up, no signs of recurrence were highlighted yet, and the cornea was still clear, with AS-OCT confirmation of pathology regression (Fig. 2). A visual acuity of 20/100 was preserved, in the absence of long-term toxicity signs affecting the anterior segment, the sclera or the lens.

Discussion

A no touch surgical excision combined with double freeze cryotherapy is traditionally the main treatment option for OSSN (Ocular Surface Squamous Neoplasia). Tumor involvement of the margins is a significant risk factor for recurrence: published data indicates that recurrence after surgical excision alone happens in about 30% of cases, and as high as 69% in those with verified positive surgical margins, whereas recurrence after wide-excisional biopsy coupled with cryotherapy stands at 8% to 16% (2,3,9).

In case of recurrent, multifocal or extensive OSSN, treatments with topical chemotherapy with MMC or 5-fluorouracil (5-FU), and immunotherapy have been used, showing good effectiveness, but increased risk of corneal damage as downside (10,15,20). Nevertheless, the optimal treatment strategy for these malignancies remains elusive because of the small patient groups reported in the literature and the lack of prospective randomized studies.

Plaque irradiation has been utilized in the past to treat microscopic tumor remnants after conjunctival OSSN surgical excision (15,16,21). In the treatment of superficial conjunctival SCCs, initial studies using beta-radiation of strontium-90 demonstrated almost 100% success rates (17). While beta radiation provides accurate low-penetration radiotherapy with precise margins, its narrow depth of field limits its use. Conversely, gamma-radiotherapy using Iodine 125 (I-125) has also been studied as an adjuvant treatment to excision for invasive conjunctival SCC due to its deeper penetration (22).

Few case series in literature reported a high range of radiation dosages (35–300 Gy) and sources (including ruthenium, strontium, and cobalt) (15,23–25). Since the radiation is absorbed at an exponential rate, inversely proportional to the distance from the seed, plaque brachytherapy appeared an ideal modality for managing surface malignancy, addressing the largest dose of radiation to the corneoscleral bed and minimizing the amount of radiation to deeper tissues (16,22). Nevertheless, some local side effects of plaque brachytherapy have been claimed, including radiation conjunctivitis, dry eye, cataract, scarring, symblepharon, ulceration, and corneal perforation (26). Immediately after plaque brachytherapy for corneal disease, recent reports highlighted a degeneration of neural structures in the applicator zone and central zone, which was charac-

terized by the total lack of sub-basal nerve fibers. Consequently, changes in corneal sensitivity were directly correlated with post-irradiation damage to the sub-basal nerve plexus and its regeneration (27).

Moreover, late scleral alterations after radiation treatment have been documented, despite scleral being generally radioresistant. Radiation-induced scleral necrosis (RISN) was seen in 5% of patients at 1 year and 12% at 5 years after plaque irradiation for ciliary body melanoma, according to research by Gündüz and colleagues (28). In contrast, in a large cohort of 4,831 eyes treated with iodine-125 brachytherapy, scleral necrosis appeared between 5 and 351 months after the treatment in 1% of cases (29,30). In our case, no signs of toxicity were reported after brachytherapy, neither in the early period affecting corneal sensitivity, nor during follow-up affecting the sclera or the anterior segment.

The combination of different strategies to achieve maximum disease control has been studied for many years, however a standardized treatment algorithm for SCC still lacks. The average recurrence rate of SCC treated by excision adjuvated by brachytherapy, among the 116 cases documented in the literature, was 6.0%. While Laskar et al. observed recurrence in 2 out of 10 SCC patients (20%), the majority of studies indicate recurrence rates of 0–14.8% (15,31,32).

Walsh-Conway et al. used I-125 irradiation to treat 6 patients with scleral-invasive conjunctival SCC. A single instance of distant conjunctival recurrence occurred throughout the course of a 23-month mean follow-up period (16). Moreover, they reported five cases of epithelial erosion in the immediate post-operative days, similar to our case, resulting from direct trauma over limbal lesions. No other major adverse effects were reported (16).

Similarly, Arepalli et al. achieved good local tumor suppression using plaque radiation with a gamma source of I-125 in 18 patients with recurrent conjunctival SCC and scleral or intraocular invasion (19). The diameter of the plaques in this report varied from 13 mm to 22 mm, and in all but three cases, they were sutured directly to the sclera; in the other cases, anterior chamber invasion necessitated suturing above the cornea. Nevertheless, in 4 instances, although local control, distant tumor growth inside the eye or orbit necessitated enucleation ($n=2$) or exenteration ($n=2$) (19).

More recently, Rao et al. used Ru-106 plaque brachytherapy in 42 eyes with OSSN causing histopathologically-proven corneal stromal or scleral invasion, following surgical excision with 4 mm clinically clear margins (33). Over a mean follow-up of 36.9 months, they reported complete tumor regression in all eyes and no evidence of regional lymph node or systemic metastasis. A good visual acuity was also maintained in a good percentage of eyes (83% with $\geq$20/200). Two eyes showed conjunctival tumor growth remote from the site of prior treatment (33).

Finally, Fagerberg et al. claimed optimal disease control with excision adjuvated by cryotherapy and plaque brachytherapy using a 106-ruthenium plaque (34).

Conclusion

In our work, we presented a case of a patient with corneo-conjunctival SCC who had already underwent numerous surgeries and topical MCC cycles with frequent recurrence of the pathology. Brachytherapy treatment showed optimal control of both corneal and conjunctival involvement, with the patient free of relapse after a 24-month follow up period. This result suggests that Ru-106 brachytherapy could be an effective option of treatment both for residual scleral-invasive conjunctival SCC following resection, and for cases of corneal tumor infiltration not responding to topical therapies. Prospective studies could be useful to define the role of AS-OCT in this subset, either as adjuvant tool to the slit lamp examination to define brachytherapy treatment plan, either in the post-operative follow up to document regression and/or recurrence of the lesion, thanks to its high sensitivity and repeatability.

Institutional review board statement

Not applicable.

Informed consent

We ensure that a statement of consent to publish these findings and images was gathered from the patient.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data availability

The data that support the findings of this study are available from the corresponding author, MMC, upon reasonable request.

Disclosures

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