



Case report

Squamous cell carcinoma of the conjunctiva. Case report

Rogers Leonardo Baquero García^{a,*}, Julián Jimenez^a, Carlos Gubbay^a,
Juan Fernando Castañeda^a, Álvaro Granados^b

^a San José Hospital, Fundación Universitaria de Ciencias de la Salud (University Foundation of Health Sciences), FUCS, Colombia

^b San Jose Hospital, Professor at Fundación Universitaria de Ciencias de la Salud (University Foundation of Health Sciences), Colombia

ARTICLE INFO

Keywords:

Squamous cell carcinoma (carcinoma)
Squamous cell
Orbit
Surgery
Radial free flap
Plastic surgery
Case report

ABSTRACT

Introduction: The prevalence of squamous cell carcinoma of the eyeball is low, and this is a rare condition. There are multiple therapeutic strategies for the treatment and depend on the degree of local involvement and extension of the tumor which, in turn, will have an impact on the patient's prognosis.

Presentation of case: We present a case of a patient with a mass of progressive growth on the left eyeball whit vision damage. The biopsy showed a squamous cell carcinoma of the conjunctiva, and imaging studies showed orbital invasion cT4bN0cM0, so surgery was indicated. The surgery was done with macroscopic margins of 5 mm. After resection, a radial free flap reconstruction was performed. Adjuvant treatment with radiotherapy was performed without complications. After six months, the patient manifested an improvement in his quality of life, and there is no evidence of relapse.

Discussion: The prevalence of squamous cell carcinoma of the conjunctiva is low. The most important risk factor is exposure to UV rays. Most are derived from conjunctival intraepithelial neoplasms. There are topical management protocols with chemotherapeutic agents and in patients with ocular or orbital invasion, enucleation and exenteration are the treatments of choice.

Conclusion: The squamous cell carcinoma of the conjunctiva is rare. The management in the locally advanced tumors is surgical. The use of a radial free flap reconstruction is one of the reconstructive strategies to take into account, and the knowledge of additional strategies required to control the disease is important to ensure an optimal treatment.

1. Introduction

Squamous cell carcinomas are the most frequent tumors on the ocular surface [1]. The most important risk factors are exposure to UV rays [2]. Most squamous cell carcinomas are derived from conjunctival intraepithelial neoplasms (CIN) [1,3], and the diagnosis of these lesions may be clinical when a patient have lesions that occur diffusely on the eyeball more than 1 mm from the corneal limbus. In the present article, the management of a patient with locally advanced squamous cell carcinoma of the left conjunctiva was performed in the San José Hospital from Bogotá, Colombia is reported. This Topic is quite rare in literature and the knowledge of its management and highlights are applicable globally.

The treatment of the locally advanced lesions is surgical and it must be considered the involvement of adjacent structures for the resection. Few patients have periocular and orbital invasion; there are isolated case reports [4]. The present case is the first confirmed report in Colombia of an invasive squamous cell carcinoma of the conjunctiva. There are not specific guidelines published in the literature about this topic. This work has been reported in line with the SCARE 2020 criteria [5].

2. Presentation of case

This was a female patient in the fourth decade of her life without medical, surgical, family, genetic, allergies, social (alcohol or smoking)

Abbreviations: ntv, ultraviolet; DNA, deoxyribonucleic acid; HPV, human papillomavirus; HIV, human immunodeficiency virus; CIN, conjunctival intraepithelial neoplasms; UK, United Kingdom; EMA, membrane epithelial antigen; Gr, grams; FRAFF, free radial artery forearm flap; Mm, millimeters; AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma; OSSN, ocular surface squamous neoplasia; OS, overall survival; DFS, disease-free survival; EBRT, External Beam Radiation Therapy; CT, computed tomography; IMRT, intensity-modulated radiation therapy.

* Corresponding author at: Calle 10 #18-75, Hospital de San José, Second floor, General Surgery Office, Bogotá 110321, Colombia.

E-mail address: rbaquero@fucsalud.edu.co (R.L.B. García).

<https://doi.org/10.1016/j.ijscr.2022.106785>

Received 5 December 2021; Received in revised form 13 January 2022; Accepted 20 January 2022

Available online 24 January 2022

2210-2612/© 2022 Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and psychosocial history, whit HIV test negative 3 months ago, who consulted on your own to the emergency room of the San Jose Hospital from Bogotá City, with a history of intraepithelial lesion of the conjunctiva of the left eye since sixth months ago, under oncological ophthalmology follow-up with rapid and progressive growth of the lesion in the last two months, over-infection, perforation of the eyeball caused by the tumor, and uveal exposure (Fig. 1) for which she was admitted to the emergency room (Fig. 2). Extension images (CT and neck sonography) were taken (Fig. 1), and the studies identified soft tissue sepsis with a high risk of meningitis, with bone involvement without intracranial compromise. Three days after admission, the ophthalmic surgeon performed an enucleation where the presence of squamous cell carcinoma of the conjunctiva was confirmed (Fig. 3). TNM classification was done with the eighth edition of American Joint Committee on Cancer (AJCC) classification: cT4bN0cM0 (Table 1) [6], and the stage is at present not recommended [6].

The antibiotic therapy to treat the soft tissue infection was completed (piperacillin/tazobactam 4.5 g each 8 h for 8 days).

The surgical procedure was performed by the head and neck surgeon two weeks after the admission in the emergency room, following the recommendations from the anesthesiologist. Prophylactic antibiotic (first generation cephalosporin) was administered according to the institutional protocol. In supine position, with hyperextension of the neck, through a maxillectomy of the suprastructure (Brown classification Tipe V) [7] with macroscopic margins of 5 mm plus superficial parotidectomy and supraomohyoid lymph node dissection (levels I, II and III) of the left neck (Figure 4). Subsequently, the reconstruction was done with a left free radial artery forearm flap (FRAFF) (Fig. 5) by reconstructive plastic surgery (arterial supply: facial artery, venous drainage: internal jugular vein) (Fig. 4). The forearm was covered with a

skin graft that was obtained from the thigh (Fig. 5). There were not complications.

Intraoperatively the margins were evaluated by palpation and taking into account the preoperative planning of the resection; circumferential enlargement samples were taken to evaluate margins through the histopathological evaluation.

The post-intervention considerations were the pain management, rehabilitation with head and neck movements, and monitoring of vitality and integration of the free flap.

Histopathological report with poorly differentiated cell non-keratinizing squamous cell carcinoma whit focal positivity for EMA and negativity for AR, ADIPOFILINA, CK7 and CK20 pT4bN0Mx (eighth edition of American Joint Committee on Cancer classification), with negative margins.

In the first month of the follow-up in the San José Hospital from Bogotá city, the patient gives us her Informed consent for this publication using the International Journal of Surgery form (written consent).

Patient showed favorable progress as well as rehabilitation in adjuvant treatment with radiotherapy without complications (IMRT total prescription dose was 66 Gy in 33 fractions at 2 Gy). Six months later without evidence of relapse in the imagenological studies (CT and neck sonography negatives). The patient is waiting for the adaptation of an eye prosthesis.

The present case is the first in Colombia of an invasive squamous cell carcinoma of the conjunctive with the use of a FRAFF.

3. Discussion

Squamous cell carcinomas of the conjunctive are rare [1]. Their incidence depends on the geographical location. It can be as low as 0.02/

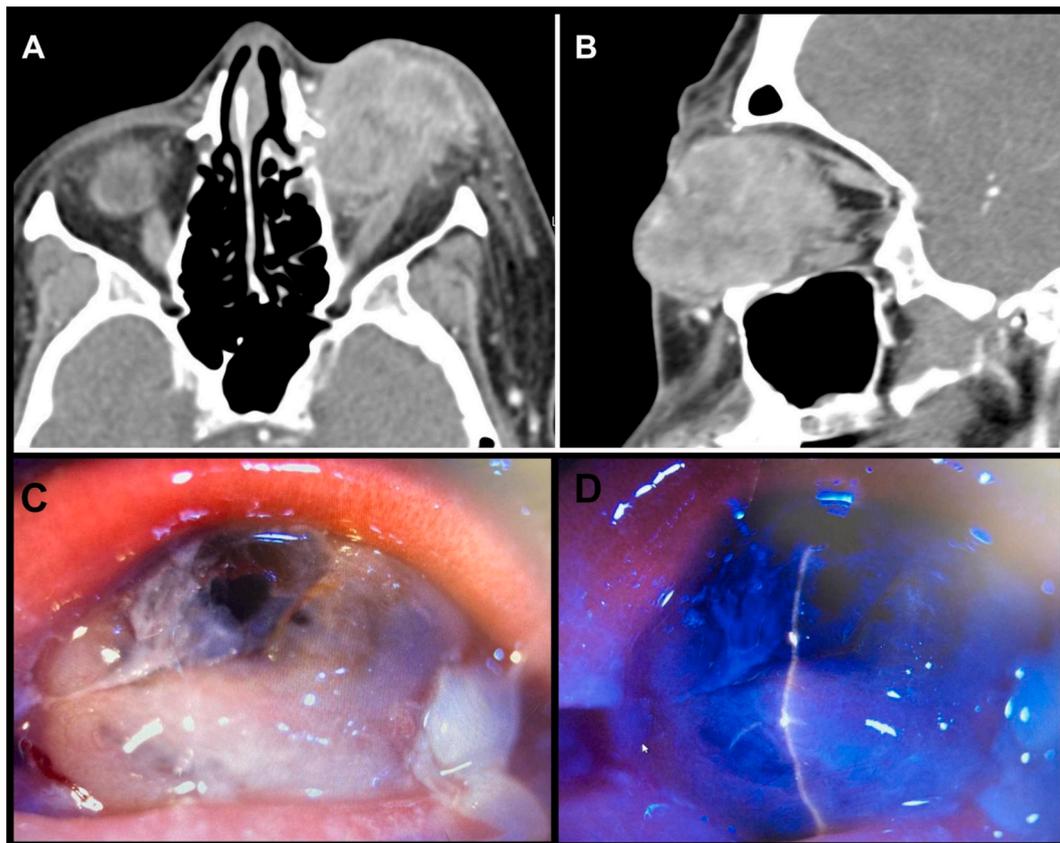


Fig. 1. Image studies and ophthalmologic examination. A. Axial section of the orbit with bone involvement. B. Sagittal section of the orbit whit orbital invasion. C and D. Ophthalmological evaluation with a brown lesion in appearance that show neovascularization. (Images authorized under the written consent of the patient). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Fig. 2. Preoperative pictures. A. Left lateral view. B. Front view with inferior tarsus involvement. C. Right lateral view. (Images authorized under the written consent of the patient).

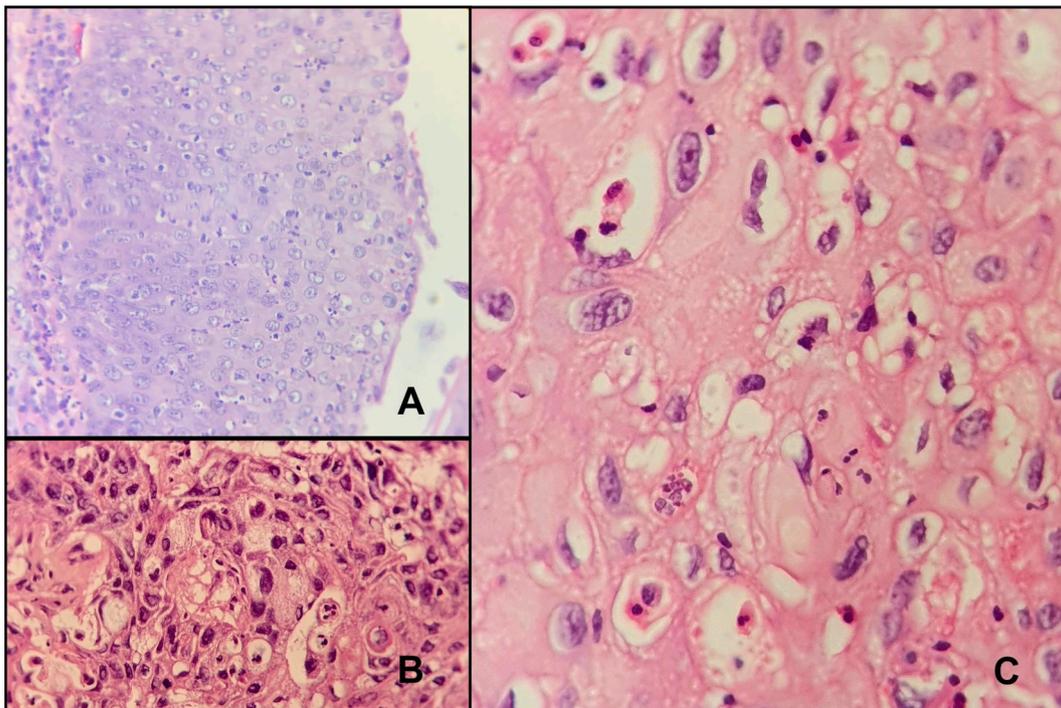


Fig. 3. A, B, C: Histopathological findings of poorly differentiated cell non-keratinizing squamous cell carcinoma of the left conjunctiva with focal positivity for EMA and negativity for AR, ADIPOFILINA, CK7 and CK20.

1,000,000 inhabitants in the UK, and as high as 12/1,000,000 inhabitants in African countries [1,3]. The conjunctival intraepithelial neoplasms (CIN) as well as other precursor lesions of this carcinoma are the leukoplakia, actinic keratosis of the conjunctiva and the papillomatous lesions, so their identification and early diagnosis allow to offer timely treatment [8,9]. In our case the patient had history of intraepithelial lesion of the conjunctiva of the left eye, with rapid and progressive growth of the lesion in two months.

The damage to the genes that code for proteins in charge of repairing DNA are altered by the direct action of UV rays on the genetic material [2,10]. Other risk factors are HPV infection, HIV infection [11] or any

state of immunosuppression, repetitive trauma, chronic eye infections (trachoma), men between 50 and 75, xeroderma pigmentosum, etc. [1]. Our patient had a HIV test negative 3 months ago.

The human papilloma virus (HPV) is carcinogenic in cervical and head and neck squamous cell carcinomas [12], but in patients with OSSN the role of HPV is still lacking (cofactor in the development of OSSN in susceptible hosts) [12,13]. In our case, HPV test was not performed in the pathology specimen.

The diagnosis of these lesions may be clinical. Characteristically, squamous cell carcinomas of the conjunctiva are lesions that occur diffusely on the eyeball more than 1 mm from the corneal limbus. They

Table 1

American Joint Committee on Cancer (Eighth edition AJCC) classification of Carcinoma of Conjunctiva (Clinical and pathological).

Clinical and pathological classification	
T- primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 5 mm or less in greatest dimension invades through the conjunctival basement membrane
T2	Tumor more than 5 mm in greatest dimension, invades through the conjunctival basement membrane without invasion of adjacent structures
T3	Tumor invades adjacent structures (1)
T4	Tumor invades the orbit or beyond
T4a	Tumor invades orbital soft tissues, without bone invasion
T4b	Tumor invades bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades brain
N- regional lymph nodes	
Nx	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M- distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

1. Adjacent structures include: the cornea, intraocular compartments, fornical conjunctiva (lower and/or upper), palpebral conjunctiva (lower and/or upper), tarsal conjunctiva (lower and/or upper), lacrimal punctum and canaliculi (lower and/or upper), plica, caruncle, posterior eyelid lamella, anterior eyelid lamella and/or eyelid margin (lower and/or upper).

are brown in appearance and show neovascularization on ophthalmological examination [14]. The ophthalmological evaluation of our patient showed a brown lesion in appearance that show neovascularization (Fig. 1). The intraocular tumor involvement occurs via direct extension of the tumor through the sclera or extension along the anterior ciliary vessels and affect the vision [15]. Our patient had loss of the vision for intraocular involvement.

Histological diagnosis becomes paramount for diagnostic confirmation and differential diagnosis. If necessary, immunohistochemical staining can be done. Here, the use of markers such as EGFR suggests the presence of basal cell carcinomas, negativity for CK7 and CK20 speaks of tumors of squamous origin, and positivity for pancytokeratin speaks of a carcinomatous differentiation [16]. The Histopathological report of this

patient showed a poorly differentiated cell non-keratinizing squamous cell carcinoma with focal positivity for EMA and negativity for AR, ADIPOFILINA, CK7 and CK20 that favors squamous cell carcinoma.

Periocular involvement (T3 and T4, Eighth edition AJCC) is presented in 1% to 6% of cases [4], and the presence of higher pathologic grade and positive pathologic margins are strong predictors for aggressive tumors [4]. In the literature, the aggressive variants were observed with more frequency in HIV positive patients [17].

The treatment of these lesions can be surgical or medical depending on the extent and involvement of structures such as the basement membrane which will not only determine the risk of metastasis, but also the risk of relapse. At the moment, there are topical management protocols with multiple chemotherapeutic agents (mitomycin, interferon alpha 2b and 5-fluorouracil) that have promising results [18,19] as well as local resection with the use of cryotherapy. However, in patients with orbital invasion or complete involvement of the conjunctiva (T3 and T4, Eighth edition AJCC), enucleation and exenteration are the treatments of choice and the GOLD standard of care [1,9,19,20]. Miller et al. found that in patients with advanced SCC (squamous cell carcinoma) surgically treated, almost 60% did not require additional surgical treatment [21]. In our case, the patient had a locally advanced squamous cell carcinoma of conjunctiva with bone involvement without intracranial compromise cT4bN0cM0. The ophthalmic surgeon performed an enucleation, and the head and neck surgeon performed the wide local resection with macroscopic margins of 5 mm. After surgery, the histopathological showed negative margins.

The free radial artery forearm flap (FRAFF) is an excellent tool in the reconstruction of head and neck defects after oncological resections, that provides well-vascularized, pliable and thin soft tissue [22]. In this case, the reconstruction was done with a left FRAFF with arterial anastomosis to the facial artery and venous anastomosis to the jugular internal vein, without complications.

Savino et al. found that the 5-year recurrence rate in patients with OSSN (T3 and T4, Eighth edition AJCC) was 64% [4]. In this study, the factors related with higher risk of recurrence were: tumor anatomical characteristics at presentation (multicentric pattern and inferior tarsus involvement), histological diagnosis of high-risk SCC and positive margins [4]. Additionally, in patients with surgery plus adjuvant therapy (chemotherapy or radiotherapy) the OS (overall survival) at 12, 24, 36, and 60 months was respectively 97.1%, 92.7%, 92.7%, and 92.7%. The DFS (disease-free survival) at 12, 24, 36, and 60 months was respectively 62.9%, 50.8%, 41.6%, and 29.7%. A short OS was observed

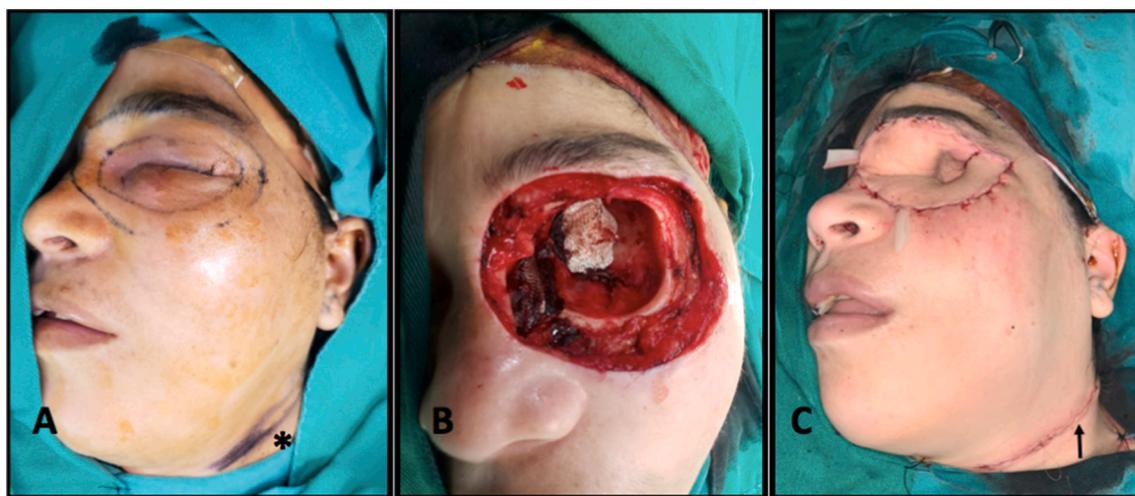


Fig. 4. Intraoperative pictures A. Surgical planning macroscopic margins of 5 mm (*: surgical planning of lymph node dissection). B. Surgical resection with maxillectomy of the suprastructure (brown classification Tipe V). C. Postoperative view (radial flap reconstruction) (arrow: postoperative view of the supraomohyoid lymph node dissection). (Images authorized under the written consent of the patient). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

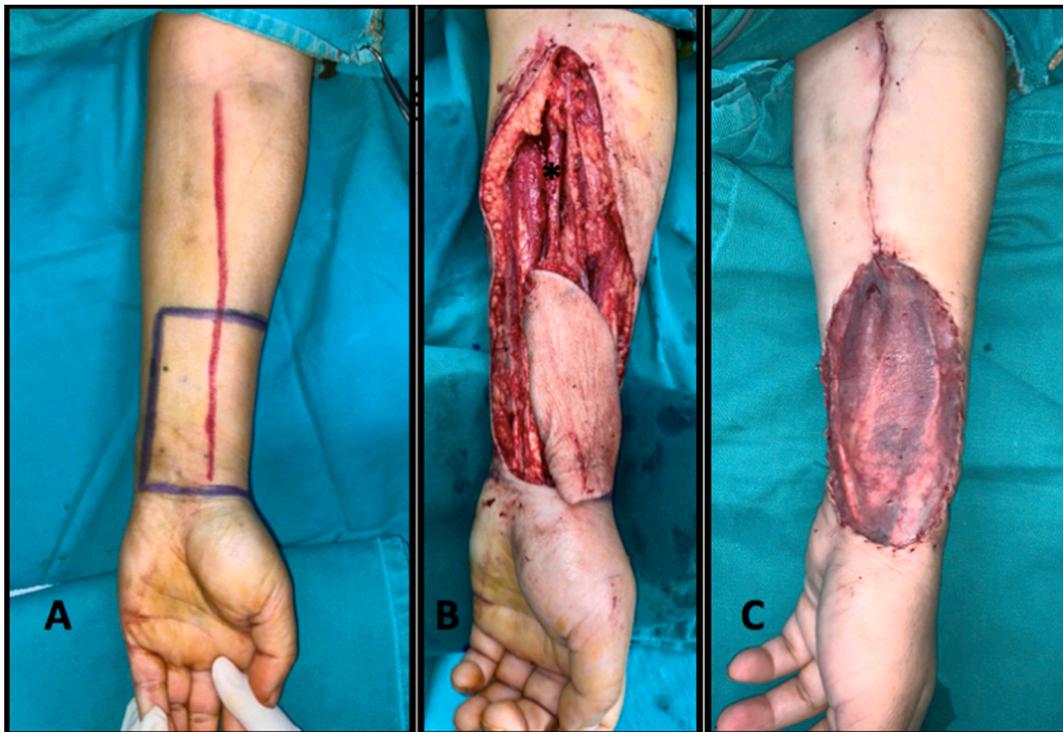


Fig. 5. Intraoperative pictures of the Free Radial Artery Forearm Flap. A. Surgical planning. B. Radial Flap (*: radial artery). C. Postoperative view of the forearm covered with a skin graft (donor site: thigh). (Images authorized under the written consent of the patient).

in patients who underwent surgery alone. [4].

Surgery alone is associated with a higher recurrence rate [23]. Adjuvant topical therapy is effective in decreasing recurrence rates (up to 15.7%) in some patients (tarsal involvement, multicentric pattern anatomical involvement, positive margins and histological high-risk SCC) [23,24]. In these patients is necessary to consider adjuvant treatments in the therapeutic strategy: EBRT (External Beam Radiation Therapy), brachytherapy, local and also systemic chemotherapy, and recently the use of PD1 inhibitors [25]. In this case, the presence of an aggressive variant (poorly differentiated), inferior tarsus involvement and multicentric compromise of the malign neoplasia indicated the need for adjuvant treatment for decrease the local-regional recurrence.

In patients with invasive disease (T3 and T4 AJCC) the chemotherapy alone is not recommended [26]. The topical chemotherapy is used preoperatively with the objective of decreasing tumor size prior to surgery (neoadjuvant); intraoperative is used as a substitute for cryotherapy, postoperative with the purpose of reducing the risk of recurrence in patients with positive surgical margins (adjuvant chemotherapy) [26,27]. When the recurrence is presented, the chemotherapy is used instead of repeat surgery [26]. At the moment, there are not randomized trials directly comparing agents of adjuvant chemotherapy for invasive SCC of the conjunctiva. For this patient, the topical chemotherapy is not indicated for the FRAFF location.

In these cases, the risk of invasion in to the orbit, perineural invasion (8% to 14%), and lymphatic or hematogenous metastasis is higher [28]. The incidence of metastasis in the regional lymph node is up to 24% with most regional metastasis occurring in the parotid and submandibular nodes [18] and distant metastasis is reported in 6.2% of cases [29]. The Anderson Cancer Center showed that patients with invasive SCC (T3 or greater AJCC) or tumor diameter larger than 18 mm had nodal metastases, and the 3-year disease-free survival rate was 79% [30].

Metastatic compromise of these lesions is unlikely, so their clinical behavior tends to be not very aggressive. However, they present a significant compromise from local infiltration. These tumors usually begin with lesions at the level of the transitional epithelium with subsequent

involvement of the cornea, the eyeball, the orbit and finally may secondarily involve the parotid gland, regional cervical nodes, lungs, and bones [1,21]. In our case, the patient had not metastatic compromise.

El-Hadad et al. showed in a retrospective recent study founded the significant association between orbital exenteration and nodal metastasis (overall risk up to 9%) and a higher risk of diseases-related death and the organ transplant like a significant risk factor for local recurrence and orbital exenteration [31]. The decision to perform a superficial parotidectomy plus supraomohyoid lymph node dissection (levels I, II and III) of the neck was supported in these topics.

In head and neck, the adjuvant radiotherapy is recommended for malignancies with perineural invasion, aggressive histologic subtype, nodal metastasis or close surgical margins to guarantee a local-regional control [32]. Only a few case reports used postoperative adjuvant EBRT in patients with SCC of conjunctiva [32,33]. Therefore, in patients with reconstructive surgery is adequate have a 6 to 7 weeks delay between surgery and EBRT [32]. Mendenhall et al. showed that adjuvant radiotherapy produced a higher local control (80%) in patients with asymptomatic perineural invasion [34]. In this case, there was not perineural invasion.

Adjuvant radiotherapy is a useful tool in the oncological management of these patients and can achieve a recurrence rate of as much as 0.02%. However, the most important prognostic factor to decrease the risk of relapse is the presence of tumor-free margins. A relapse rate of 5% has been documented compared to a relapse risk of up to 50% in patients with positive tumor margins [1,16]. In our case, the margins were negative and the adjuvant treatment with radiotherapy there had not complications.

Cruzado et al. reported a series of cases in a referral hospital for ocular malignancies in Perú [35]. This is the largest series in Latin America to date. Characteristics were identified in this retrospective case series study that may resemble those that could be found in our population. A total of 176 cases over a 20-year period with their respective follow-up were included. A preference for the male sex was

identified with no differences with respect to the laterality of the tumor. The most common treatment offered in this series was exenteration of the lesion followed by tumor resection. The recurrence reported in this study was 6%. Locoregional metastatic involvement was present in 8% of the cases at the time of diagnosis, so adjuvant radiotherapy was indicated for this group of patients. One of the most important findings was that 17% of the patients presented the previous presence of a skin lesion with malignant behavior as comorbidity [15] which suggests a direct relationship between exposure to UV radiation and the development of this type of malignancy as an important risk factor.

The expectative and perspective of the patient were favorable, and the patient is waiting for the adaptation of an eye prosthesis.

4. Conclusion

The squamous cell carcinoma is the most common non-melanocytic neoplasm of the surface of the eyeball, yet it remains a rare condition. As with the rest of squamous cell carcinomas, UV exposure that causes damage to the genes which enable DNA damage caused by radiation to be repaired is one of the risk factors. The treatment of locally advanced squamous cell carcinomas is still a surgical approach, and this should achieve a disease-free resection as this will have an impact on the prognosis and disease-free time and survival of these patients. The available adjuvant therapy strategies should be had in count for decrease the local-regional recurrence rates.

Funding

Not applicable.

Ethical approval

Not applicable, this is not a research project.

Informed consent

Written informed consent was obtained from the patient during the follow-up for publication of this case report and accompanying images using the International Journal of Surgery form. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Rogers Baquero: Writing- Original draft, visualization, supervision, project administration, Review & Editing.

Julián Jimenez: Investigation, methodology.

Carlos Gubbay: Conceptualization, Investigation.

Juan Castañeda: Conceptualization, Investigation, Review & Editing.

Álvaro Granados: Supervision, project administration.

Registration of research studies

Not applicable.

Guarantor

Rogers Leonardo Baquero García.

Álvaro Granados.

Statement above references

Provenance and peer review not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors have no conflict of interest.

References

- [1] Jean M.D. Yang, C. Stephen M.D. Foster, v. Int. Ophthalmol. Clin. 37 (4) (Fall 1997) 73–85, <https://doi.org/10.1097/00004397-199703740-00007>.
- [2] L. Asnaghi, H. Alkatan, A. Mahale, M. Othman, S. Alwadani, H. Al-Hussain, et al., Identification of multiple DNA copy number alterations including frequent 8p11.22 amplification in conjunctival squamous cell carcinoma, Invest. Ophthalmol. Vis. Sci. 55 (12) (2014) 8604–8613, <https://doi.org/10.1167/iovs.14-14920>.
- [3] G.A. Lee, L.W. Hirst, Ocular surface squamous neoplasia, Surv. Ophthalmol. 39 (6) (1995) 429–450, [https://doi.org/10.1016/S0039-6257\(05\)80054-2](https://doi.org/10.1016/S0039-6257(05)80054-2).
- [4] G. Savino, G. Cuffaro, M. Maceroni, et al., Advanced ocular surface squamous cell carcinoma (OSSC): long-term follow-up, Graefes Arch. Clin. Exp. Ophthalmol. 259 (2021) 3437–3443, <https://doi.org/10.1007/s00417-021-05264-3>.
- [5] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical Case Report (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230, <https://doi.org/10.1016/j.ijsu.2020.10.034>.
- [6] M.B. Amin, S.B. Edge, F.L. Greene, AJCC Cancer Staging Manual, 8th ed., Springer, New York, 2017. <https://link.springer.com/book/9783319406176>.
- [7] Q. Sun et al. Does the Brown classification of maxillectomy defects have prognostic prediction for patients with oral cavity squamous cell carcinoma involving the maxilla?. Int. J. Oral Maxillofac. Surg., Volume 49, Issue 9, 1135 - 1142. DOI: 10.1016/j.ijom.2020.01.021.
- [8] C.L. Shields, A.E. Alset, N.S. Boal, M.G. Casey, A.N. Knapp, J.A. Sugarman, Conjunctival Tumors in 5002 Cases. Comparative Analysis of Benign Versus Malignant Counterparts. The 2016 James D. Allen Lecture, Am J. Ophthalmol. 173 (2017) 106–133, <https://doi.org/10.1016/j.ajo.2016.09.034>. S0161–6420.
- [9] M.C. Coroi, E. Roşca, G. Muşiu, T. Coroi, Squamous carcinoma of the conjunctiva, Romanian J. Morphol. Embryol. 52 (1 Suppl) (2011) 513–515. PMID: 21424104.
- [10] Charles Ateenyi-Agaba, Min Dai, Florence Le Calvez, Edward Katongole-Mbidde, Anouk Smet, Massimo Tommasino, Silvia Franceschi, Pierre Hainaut, Elisabete Weiderpass, TP53 mutations in squamous-cell carcinomas of the conjunctiva: evidence for UV-induced mutagenesis, v. Mutagenesis 19 (5) (September 2004) 399401, <https://doi.org/10.1093/mutage/geh048>.
- [11] M. Guech-Ongey, E.A. Engels, J.J. Goedert, R.J. Biggar, S.M. Mbulaiteye, Elevated risk for squamous cell carcinoma of the conjunctiva among adults with AIDS in the United States, Int. J. Cancer 122 (11) (2008) 2590–2593, <https://doi.org/10.1002/ijc.23384>.
- [12] N. Di Girolamo, Association of human papilloma virus with pterygia and ocular-surface squamous neoplasia, Eye (Lond) 26 (2) (2012) 202–211, <https://doi.org/10.1038/eye.2011.312>.
- [13] Ibrahim O. Sayed-Ahmed, Sotiria Palioura, Anat Galor, Carol L. Karp, Diagnosis and medical Management of Ocular Surface Squamous Neoplasia, Expert Rev. Ophthalmol. (2016), <https://doi.org/10.1080/17469899.2017.1263567>.
- [14] Carol L. Shields, Jason L. Chien, Thamolwan Surakiatchanukul, Kareem Sioufi, Sara E. Lally, Jerry A. Shields, Conjunctival tumors: review of clinical features, risks, biomarkers, and outcomes—the 2017 J. Donald M. Gass Lecture, Asia Pac. J. Ophthalmol. 6 (2) (March 2017) 109–120, <https://doi.org/10.22608/APO.201710>.
- [15] U. Patel, C.L. Karp, S.R. Dubovy, Update on the management of ocular surface squamous neoplasia, Curr. Ophthalmol. Rep. 9 (2021) 7–15, <https://doi.org/10.1007/s40135-020-00260-y>.
- [16] J.C. Erie, R.J. Campbell, T.J. Liesegang, Conjunctival and corneal intraepithelial and invasive neoplasia, Ophthalmology 93 (2) (1986) 176–183, [https://doi.org/10.1016/S0161-6420\(86\)33764-3](https://doi.org/10.1016/S0161-6420(86)33764-3).
- [17] A. Galor, C.L. Karp, P. Oellers, et al., Predictors of ocular surface squamous neoplasia recurrence after excisional surgery, Ophthalmology 119 (10) (2012) 1974–1981, <https://doi.org/10.1016/j.ophtha.2012.04.022>.
- [18] Grace Huang, Neena Mirani, Adrian Connally, Paul D. Langer, Successful treatment of extensive squamous cell carcinoma of the conjunctiva and upper eyelid skin with topical therapy alone, Ophthal. Plast. Reconstr. Surg. 33 (3S) (May/June 2017), <https://doi.org/10.1097/IOP.0000000000000601> p S4-S6.
- [19] A. Santoni, J. Thariat, C. Maschi, J. Herault, S. Baillif, S. Lassalle, et al., Management of invasive squamous cell carcinomas of the conjunctiva, Am J. Ophthalmol. 200 (2019) 1–9, <https://doi.org/10.1016/j.ajo.2018.11.024>.
- [20] J.A. Shields, C.L. Shields, C. Suvarnamani, M. Tantisira, P. Shah, Orbital exenteration with eyelid sparing: indications, technique and results, Ophthalmic Surg. 22 (1991) 292–297, <https://doi.org/10.3928/1542-8877-19910501-13>.
- [21] C.V. Miller, A. Wolf, A. Kligenstein, C. Decker, A. Garip, A. Kampik, et al., Clinical outcome of advanced squamous cell carcinoma of the conjunctiva, Eye (Lond) 28 (8) (2014) 962–967, <https://doi.org/10.1038/eye.2014.79>.
- [22] D.S. Soutar, L.R. Scheker, N.S. Tanner, I.A. McGregor, The radial forearm flap: a versatile method for intra-oral reconstruction, Br. J. Plast. Surg. 36 (1983) 1–8, [https://doi.org/10.1016/0007-1226\(83\)90002-4](https://doi.org/10.1016/0007-1226(83)90002-4).
- [23] M.A. Blasi, M. Maceroni, M.G. Sammarco, M.M. Pagliara, Mitomycin C or interferon as adjuvant therapy to surgery for ocular surface squamous neoplasia: comparative study, Eur. J. Ophthalmol. 28 (2) (2018) 204–209, <https://doi.org/10.5301/ejo.5001035>.
- [24] A. Rajeh, F. Barakat, S. Khurma, et al., Characteristics, management, and outcome of squamous carcinoma of the conjunctiva in a single tertiary cancer center in

- Jordan, *Int. J. Ophthalmol.* 11 (7) (2018) 1132–1138, <https://doi.org/10.18240/ijo.2018.07.10>.
- [25] H. Demirci, V.M. Elnor, F.Y. Demirci, D.R. Robinson, A. Chinnaiyan, D. Schlachter, S. Joseph, F. Worden, Immunotherapy for conjunctival squamous cell carcinoma with orbital extension, *Ophthalmology* (2020) 30932–30935, <https://doi.org/10.1016/j.ophtha.2020.09.027>. S0161–6420.
- [26] R. Sepulveda, J. Pe'er, E. Midená, et al., Topical chemotherapy for ocular surface squamous neoplasia: current status *British J. Ophthalmol.* 94 (2010) 532–535, <https://doi.org/10.1136/bjo.2009.160820>.
- [27] J. Frucht-Pery, Y. Rozenman, J. Pe'er, Topical mitomycin-C for partially excised conjunctival squamous cell carcinoma, *Ophthalmology* 109 (2002), 548e52, [https://doi.org/10.1016/s0161-6420\(01\)00967-8](https://doi.org/10.1016/s0161-6420(01)00967-8).
- [28] M.J. Donaldson, T.J. Sullivan, K.J. Whitehead, et al., Squamous cell carcinoma of the eyelids, *Br. J. Ophthalmol.* 86 (2002) 1161–1165, <https://doi.org/10.1136/bjo.86.10.1161>.
- [29] M. Faustina, R. Diba, M.A. Ahmadi, et al., Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma, *Ophthalmology* 111 (2004) 1930–1932, <https://doi.org/10.1016/j.ophtha.2004.02.009>.
- [30] Vivian T. Yin, Helen A. Merritt, Matt Sniegowski, Bitá Esmaeli, Eyelid and ocular surface carcinoma: diagnosis and management, *Clin. Dermatol.* 33 (2015) 159–169, <https://doi.org/10.1016/j.clindermatol.2014.10.008>.
- [31] Christian El-Hadad, Maria Laura Rubin, Priya Nagarajan, Joshua Richard Ford, Shiqiong Xu Jr., Jing Ning, Bitá Esmaeli, Prognostic factors for orbital exenteration, local recurrence, metastasis, and death from disease in conjunctival squamous cell carcinoma, *Ophthalm. Plast. Reconstr. Surg.* 37 (2021) 262–268, <https://doi.org/10.1097/IOP.0000000000001798>.
- [32] A. Hsu, S.J. Frank, M.T. Ballo, et al., Postoperative adjuvant external-beam radiation therapy for cancers of the eyelid and conjunctiva, *Ophthalm. Plast. Reconstr. Surg.* 24 (2008) 444–449, <https://doi.org/10.1097/IOP.0b013e3181818be098>.
- [33] J. Petsuksiri, S.J. Frank, A.S. Garden, et al., Outcomes after radiotherapy for squamous cell carcinoma of the eyelid, *Cancer* 112 (2008) 111–118, <https://doi.org/10.1002/cncr.23143>.
- [34] W.M. Mendenhall, R.J. Amdur, L.S. Williams, A.A. Mancuso, S.P. Stringer, Mendenhall N. Price, Carcinoma of the skin of the head and neck with perineural invasion, *Head Neck* 24 (2002) 78–83, <https://doi.org/10.1097/01.coc.0000251224.16075.60>.
- [35] D. Cruzado-Sanchez, W.A. Tellez, B. Villarreal-Aguilar, M. Melendez, A. Olivera, F. Moran, et al., Conjunctival squamous cell carcinoma: prognostic factors for the recurrence and metastasis and clinicopathological characteristics at an oncological hospital in Peru, *Br. J. Ophthalmol.* 104 (7) (2020) 1010–1015, https://doi.org/10.4103/tjo.tjo_26_21.