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Conjunctival melanoma following cornea transplant from a cancer donor: A case report

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ABSTRACT

Purpose: Conjunctival melanoma is a rare ocular tumor. We report a case of ocular conjunctival melanoma during topical immunosuppression, after a corneal transplant from a donor with metastatic melanoma.

Observation: A 59-year-old white male presented with a progressive nonpigmented conjunctival lesion in his right eye. He had previously undergone two penetrating keratoplasties, and he was being treated with topical immunosuppression with 0.03% tacrolimus (Ophthalmos Pharma; Sao Paulo, SP/Brazil). The histopathology evaluation revealed the nodule to be a conjunctival epithelioid melanoma. The donor's death cause was disseminated melanoma.

Conclusion and importance: The correlation between cancer and systemic immunosuppression after a solid organ transplant is widely known. The local influence, however, has not been reported. In this case, a causal relationship was not established. The correlation between conjunctival melanoma, exposure to topical tacrolimus immunosuppressive therapy, and the malignance characteristic of donor cornea should be better evaluated.

1. Introduction

Melanoma is the most common primary intraocular tumor in adults, although the conjunctival one is rare and corresponds to 3–7% of all ocular melanomas and only 0.25% of all melanomas overall.[1–3] Conjunctival melanoma can arise from primary lesions, such as acquired melanosis (PAM) with atypia and conjunctival nevus, or it can develop *de novo* without any primary lesion.[4] Systemic and local circumstances, such as the presence of immunosuppression, might influence it. Cancer transmission through corneal transplantation has been reported before, although it seems to be very rare.[5,6]

We report a case of *de novo* conjunctival melanoma arising in a patient treated with local immunosuppressive therapy due to previous high-risk penetrating keratoplasty and a donor cornea from a patient with skin metastatic melanoma.

2. Case presentation

A 59-year-old Caucasian male with keratoconus and a history of right eye regraft due to previous penetrating keratoplasty (PK) failure being treated with topical 0.03% tacrolimus (Ophthalmos Pharma; Sao Paulo, SP/Brazil) BID therapy presented with a progressive nodular conjunctival lesion. His first and second PKs were 30 years and 19 months before his symptoms, respectively, and he started on topical tacrolimus therapy after the second surgery (19 mo.). The best-corrected visual acuity was 20/30 (Snellen 0.67). The right-eye conjunctival lesion was a 4 mm nonpigmented pink nodule at the inferior limbus at the five to 6 o'clock position (Fig. 1); it developed approximately between the 18 and 19 months of tacrolimus therapy, with rapid growth in the 15 days prior to the visit. There was no fluorescein staining and no blanching with topical 10% phenylephrine. The iris color was brown, and no other lesion was identified. Indirect ophthalmoscopy of the entire fundus showed no retinal or choroidal changes. The patient was in regular follow-ups with a single ophthalmologist, and no lesion was reported in

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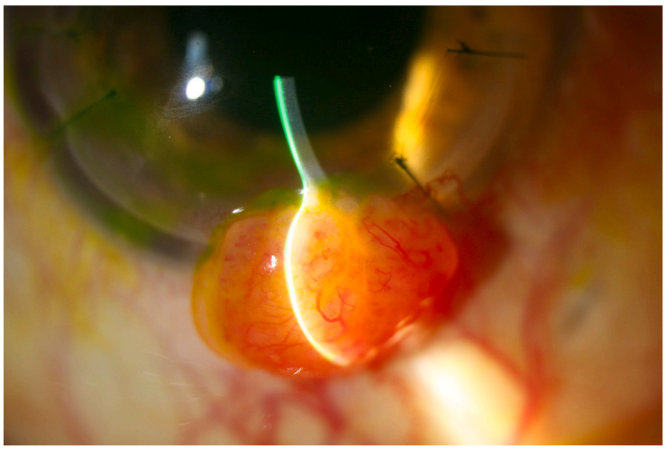

Fig. 1. Clinical evaluation of the right-eye conjunctival lesion: a 4 mm non-pigmented pink-nodule at the inferior limbus at the five to 6 o'clock position. There is no fluorescein staining. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the last visit six months before the nodule started. The histopathologic evaluation of his last transplant (19mo.) showed a failed graft without additional lesions.

The patient underwent surgical removal of the conjunctival lesion. Intraoperatively, the lesion was adhered deeply to the limbus but not to the cornea. The histopathologic evaluation revealed an amelanotic conjunctival melanoma with central ulceration without invasion of the substantia propria or the adjacent cornea (Fig. 2). The tumor had a high mitotic index (13/mm^2), according to the grading of the College of American Pathologists.[7]

After the histopathologic analysis, the patient underwent a second surgery to enlarge the surgical margins. Four biopsies of the conjunctival fornix were also taken, with no histopathologic disorders found. He had his preauricular, submandibular, and cervical lymph nodes checked, and he had no evidence of nodal involvement. Systemic clinical and imaging investigations were negative, and no lesions were found in the brain, chest, or abdomen (Computerized tomography scan). The patient had no previous ocular precursor lesions, such as conjunctival nevus or primary acquired melanosis. He had no previous history of cancer. The tumor represents a stage pTis tumor according to the pathologic tumor classification of the American Joint Committee on Cancer (AJCC) and systemic classified as a T1aN0M0 stage for conjunctival melanoma.[8]

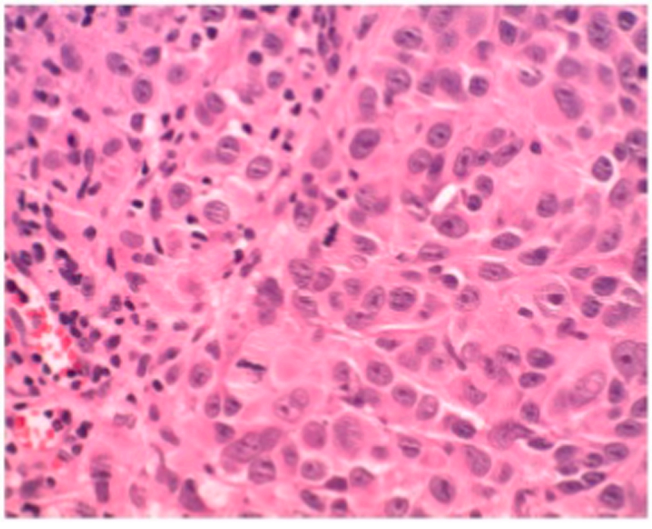

Fig. 2. Histopathological evaluation with hematoxylin and eosin staining. The evaluation showed solid neoplasia with clear cytoplasm and epithelioid cells arranged in nests, nuclei presenting anisokaryosis, and prominent nucleoli, nuclear pseudoinclusion.

The patient discontinued the topical tacrolimus and got into adjuvant therapy with 0.02% topical interferon and 1% prednisolone topical therapy BID for three months. He was monitored via monthly follow-up visits for the first six months. After that, the patient has been seen twice a year and advised to return early if necessary. At a 72-month post-melanoma resection, there was no new lesion in any part of his eye or body.

The donor's death cause was metastatic melanoma. There was no mention of the presence of metastasis in the eye of the donor. The most preferred cornea preparation in our location is removing the entire globe from the donor. Neither donor-detailed histologic examination nor tumor markers were evaluated to confirm if both tumors had the same origin because of a chronologic dissociation.

All the surgical procedures were conducted by a single surgeon (S.K.) under sterile technique and topical anesthesia.

Written informed consent was obtained from patient and the study adhered to the tenets of the Declaration of Helsinki.

3. Discussion and conclusions

Conjunctival melanoma is rare,[1–3] and its incidence varies worldwide to approximately 0.2–0.8 per million in the Caucasian population[1,3] and it seems to be similar among men and women.[1,9,10] The incidence of uveal melanoma has been stable in the past few decades, whereas cutaneous and conjunctival melanoma have shown increasing incidence rates in the same period,.[1,10] The increasing incidence of conjunctival melanoma might be related to environmental changes and extrinsic factors.[1,10,11]

Conjunctival melanoma originates from melanocytes located among the basal cells of the conjunctival epithelium, and the development of *de novo,* without any preceding lesion, is seen in 18–30% of tumors.[1,4,12] The most common ocular findings are visible spots or lumps, redness, pain, irritation or no symptoms.[4,13] It can appear as a nodular or flat lesion, with pigmentation or no pigmentation, and with dilated feeder vessels on any part of the conjunctiva; the bulbar conjunctiva close to the limbus is the most common location for presentation.[1,4] The tumor can grow locally and spread on the eye surface or infiltrate the globe or orbit (2%), nasolacrimal system and sinuses (1–5%); additionally, it can metastasize via the lymphatic system or hematogenously.[1,4,14] Limbal tumors may invade the cornea, and the intact Bowman's membrane plays a role as an essential natural barrier.[14] Metastasis occurs in approximately 16% of patients after 5 years[4,12,14] and local recurrence in 36–62% of patients.[1,14] Melanoma arising *de novo* is associated with an increased risk of metastasis and death,[1,4,13] as well as those in a forniceal location and nodular melanomas.[4]

Tacrolimus (FK506) is an immunosuppressive drug, a macrolide derived from the soil fungus *Streptomyces tsukubaensis*, and it is preferred to corticosteroids for patients in need of long-term therapy.[15] The efficacy of tacrolimus in preventing graft rejection has been shown,[16,17] and it is also less prone to an increase in intraocular pressure.[18] The main side effects of tacrolimus happen when taking it systemically.[19,20] Locally, the side effects are superficial punctate keratitis, conjunctival injection, burning sensations, superficial opacification and erosion or delay in re-epithelization. In March 2005, a U.S. Food and Drug Administration (FDA) black box warning of cancer risks was required for topical tacrolimus after 19 post-marketing cases into dermatological uses.[21] After evaluation, different studies have shown that exposure to dermatological topical tacrolimus may be associated with an increased risk of T cell lymphoma,[22,23] but not with malignant melanoma or an increase in the overall cancer rate, and the relationship between topical calcineurin inhibitors and cancer should be better evaluate.[21] Ocular cancer, including conjunctival intraepithelial neoplasia,[24] conjunctival squamous cell carcinoma[25] and ocular surface squamous neoplasia,[26]

has been described in patients under systemic immunosuppression for an organ transplant, but it has not been reported in a patient undergoing topical tacrolimus therapy.

On the other hand, some authors have discussed the possibility of transmission of malignant tumors through corneal transplantation. Still, the literature contains minimal comment on this subject, and only two cases of cancer transmitted by corneal graft have been described. The first one in 1939, a report by Hata,[27] showed the development of retinoblastoma in an eye that had received a cornea from a donor with proven retinoblastoma. The second one was in 1994, when an adenocarcinoma of the iris developed 19 months after corneal transplantation from a donor who died of disseminated adenocarcinoma. Histologic examination of the iris tumor in the recipient and the tumor biopsy from the donor revealed similar morphology.[28] Recently, there has been reported a case of donor-derived conjunctival-limbal melanoma after a keratolimbal allograft. The patient developed a limbal lesion while into systemic immunosuppression, and within one week after discontinuing it, the lesion demonstrated a dramatic improvement in size.[29]

Corneas from donors with systemic malignancies are usually accepted for transplantation. Salame et al.[6] looked at those receptors and found no difference in cancer occurring in the recipients after receiving a cornea from a donor with cancer. In a second study, the corneas of patients dying from cancer without any macroscopic evidence of ocular infiltration were evaluated, and the receivers were followed up for 5 years. Micrometastases were found in the histological sections in only two eyes corresponding to two donors, representing 1% of the 204 cancer donors and 0.5% of the 408 eyes analyzed. No cancer was transmitted in any of the 325 corneal recipients.[5] The Current recommendations of the Eye Bank Associations of America and the European Eye Bank Association permit the use of corneas from donors dying of malignancy except for malignant tumors of the anterior ocular segment, retinoblastoma, active leukemia, and disseminated lymphomas.[30]

The first attempt to report this case was to evaluate the possible correlation of conjunctival melanoma arising *de novo* in a patient with local immunosuppression. The donor's information was reached out when reviewing this manuscript as per the reviewer's suggestion, and we were surprised with a donor cancer case. The temporal correlation between the surgeries and reaching the donor information was longer than two years, so, unfortunately, we couldn't run further tests on donor tissue.

We cannot affirm that the melanoma was neither transmitted by the donor nor facilitated by the topical therapy, although the facts might not be only a coincidence. Donor-recipient tumor transmission through corneal transplantation is highly improbable when the eyes are free of cancer. Still, the combination of the malignancy infiltration from the donor and the local immunosuppression may have played a role in this case. There are also likely environmental and genetic factors that are still misunderstood, and more studies are needed to evaluate them further.

Declarations and patient consent

The study adhered to the tenets of the Declaration of Helsinki.
The patient formally assigned the written consent for publication.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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List of abbreviations

AJCC	American Joint Committee on Cancer
SCC	Squamous cell carcinoma
BCC	Basal cell carcinoma
CsA	A-cyclosporine
FDA	Food and Drug Administration

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