Donor-Derived Conjunctival-Limbal Melanoma After a Keratolimbal Allograft

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Purpose: To report a single case of donor-derived conjunctival–limbal melanoma that occurred after a keratolimbal allograft (KLAL).

Methods: Case report and literature review.

Results: A 56-year-old white woman with a history of bilateral limbal stem cell deficiency developed a donor-related melanoma after a KLAL. Three months after undergoing an uncomplicated KLAL, the patient presented with hemorrhagic nodules within her conjunctiva and transplanted tissue. Excisional biopsy was performed, and the pathology results revealed melanoma cells. Although the donor of the KLAL had a history of metastatic melanoma, the ocular tissue was in compliance with all eye bank requirements for donation. After discovery of the tumor, the patient's systemic immunosuppression was stopped. Within 1 week, the patient demonstrated a dramatic improvement in the size of the lesion. One month after the initial biopsy, the KLAL tissue was excised, and a pathology report revealed that there were no viable tumor cells on the ocular surface. As the limbal stem cell deficiency recurred, the eye underwent placement of a Boston type 1 keratoprosthesis.

Conclusions: We present a case of conjunctival–limbal melanoma after a KLAL from a donor who had a history of metastatic melanoma. In response to this case, the US eye banking guidelines were amended to include stricter parameters for vascularized ocular tissue transplantation.

Key Words: donor-derived tumor, melanoma, keratolimbal allograft, ocular surface stem cell transplantation, systemic immunosuppression

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The incidence of melanoma is increasing rapidly. In Europe, over 100,000 individuals develop melanoma every year.[1] The American Cancer Society estimated that there were 73,870 new cases of skin melanoma in 2015 (American Cancer Society, http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf, accessed May 16, 2016).

Tumor dormancy of melanoma may be related to immune-mediated mechanisms (cell cycle arrest, immune surveillance, and blocked angiogenesis), inducing a dormant equilibrium state.[2] Melanoma may remain dormant for an extended period in the immunocompetent host, yet it can reactivate as a late recurrence, metastatic disease, or de novo malignancy under the influence of immunosuppression.[2]

Donor-related transmission of malignancy from organ transplantation is an uncommon but potentially devastating complication that was first reported in 1965.[3,4] Transmission of cutaneous melanoma by organ transplantation has been documented multiple times since it was first described in 1972.[5]

The current recommendations for accepting a donor with a history of malignancy for solid organ transplantation are based predominantly on single-case reports. Published guidelines for screening of donor organs have been inconsistent.[6] Currently, in the United States, there are limited restrictions on the transplantation of ocular tissue derived from donors with a history of malignant disease. Before this case, the only donors who were deemed ineligible to donate were those with a history of leukemia, lymphoma, adenocarcinoma of the eye, retinoblastoma, and anterior segment tumors.[7] We present the first reported case of donor-derived transmission of melanoma in a patient who underwent a keratolimbal allograft (KLAL).

CASE REPORT

A 56-year-old white woman presented with a 25-year history of soft contact lens wear. On initial examination, the patient had total limbal stem cell deficiency with resultant ocular surface failure of both eyes; visual acuity was 20/125 and 20/60 in the right and left eyes, respectively. After discussing the risks, benefits, and alternatives, the patient opted to undergo a KLAL of her right eye. The patient did not have any living related donors who could donate tissue; therefore, the KLAL procedure was recommended. Two weeks before her surgery, systemic immunosuppression with mycophenolate mofetil 500 mg and tacrolimus 4 mg twice daily was initiated. The patient underwent uncomplicated KLAL transplantation. One month postoperatively, the patient had successful restoration of her ocular surface with 20/40 visual acuity.

One month later, the patient seemed to have acute rejection of one of the KLAL segments, with increased injection and neighboring subconjunctival hemorrhage. The patient was administered oral prednisone, and her topical corticosteroid eye drops were increased.

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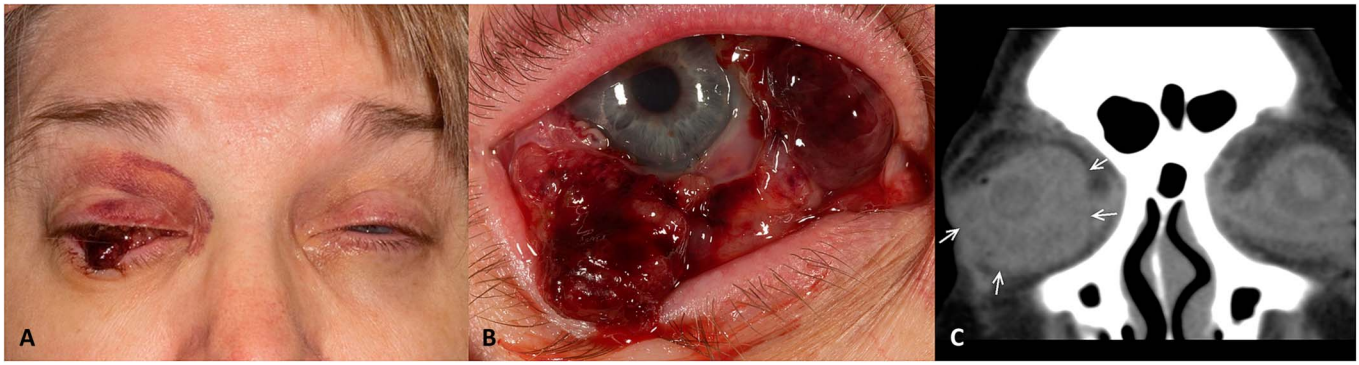

FIGURE 1. Two and a half months after KLAL, our patient presented with diffuse subconjunctival hemorrhage and a nodular lesion of the conjunctiva (A, B). CT of the orbits (coronal scan) revealed an anterior orbital mass extending into the Tenon space for 360 degrees, most prominently involving the medial, inferior, and lateral quadrants (arrows, C).

Two weeks later, the patient presented with diffuse subconjunctival hemorrhage and a nodular lesion of the conjunctiva (Figs. 1A, B). Computer tomography (CT) of the orbits (Fig. 1C) revealed an anterior orbital mass extending into the Tenon space for 360 degrees, most prominently involving the medial, inferior, and lateral quadrants. The axial scans (not shown) demonstrated extension to the rectus muscles insertions but no further posteriorly. The medical history of the KLAL donor had been significant for dual malignancies, cutaneous melanoma and breast cancer. The following day, the patient underwent incisional biopsy and tumor debulking. A pathology report revealed melanoma cells (Fig. 2). Additional testing disclosed strong diffuse positive staining for S100, Mart-1, and Sox10 (Fig. 3); there was also moderate diffuse positive cytoplasmic staining for HMB-45. These are all markers for melanocytic cells. A positron emission tomography scan of the whole body did not reveal any distant metastases.

The patient was referred to a hematology/oncology specialist and an ocular oncologist. Treatment recommendations from oncology and ocular oncology included topical immunotherapy/chemotherapy, external beam radiation (dosage intended to be curative), adjuvant external beam radiation before enucleation, or eyelid-sparing exenteration. Our renal/organ transplantation immunosuppression specialist recommended against enucleation, exenteration, radiation, and systemic chemotherapy as initial therapy. Conversely, he recommended abrupt discontinuation of systemic immunosuppression and escalating therapy depending on the patient's response.

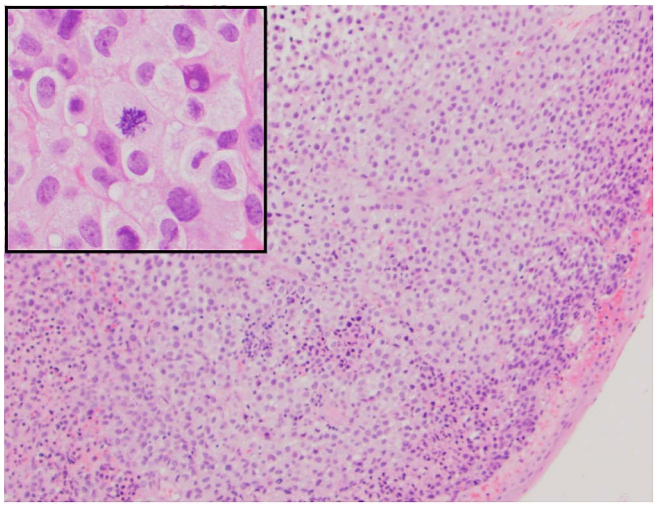

FIGURE 2. Low magnification (×100) hematoxylin and eosin stain of incisional biopsy demonstrating round to polygonal cells of intermediate size in diffuse sheets; high magnification (×400) shows numerous mitotic figures (inset).

Within 1 week of stopping systemic immunosuppression, the patient demonstrated a dramatic reduction in signs and symptoms (Fig. 4A). Based on recommendations from ocular oncology, the patient was placed on topical mitomycin C 4 times daily for 2 weeks. Because of residual pigmented cells being visible in the KLAL tissue, the patient underwent excision of the KLAL segments and any visibly involved tissue 3 weeks after the incisional biopsy. The tissue was sent for pathology, and necrotic tissue with no viable tumor cells was revealed.

Fourteen months after the incisional biopsy, the patient has remained clear of any signs or symptoms of recurrence (Fig. 4B). As there was expected recurrence of the limbal stem cell deficiency (no viable stem cells secondary to previous long-term contact lens wear), the patient chose to undergo placement of a Boston type 1 keratoprosthesis (KPro) 6 months after KLAL resection (Fig. 4C). Follow-up CT of the orbits 2 months after the KLAL excision revealed no evidence of mass and unremarkable orbital structures. The patient has continued to follow up with a local oncologist for ongoing surveillance. They have monitored the complete blood count, comprehensive metabolic panel, and lactate dehydrogenase; CT of the orbits, chest, abdomen, and pelvis 6 months after KLAL excision and CT of the abdomen with chest x-ray at 13 months after KLAL excision demonstrated no evidence of metastatic disease. The patient will now obtain surveillance imaging based on clinical symptoms. Ten months after KPro placement, the patient has remained stable with 20/60 visual acuity.

DISCUSSION

Since the beginning of solid organ transplantation, an increased risk of cancer after transplantation has been documented. This elevated risk is the result of several factors, including immunosuppression from antirejection medications, decreased control of oncogenic viral infections, and underlying medical conditions common to transplantation recipients.[8] The risk of transplanting a malignancy to the recipient from the donor is less common. In a series of 108,062 transplant recipients, a total of 21 donor-related malignancies were reported (type of transplant: 8 liver, 10 kidney, 2 heart, and 1 pancreas); of these, 4 malignancies were melanoma by histology.[9]

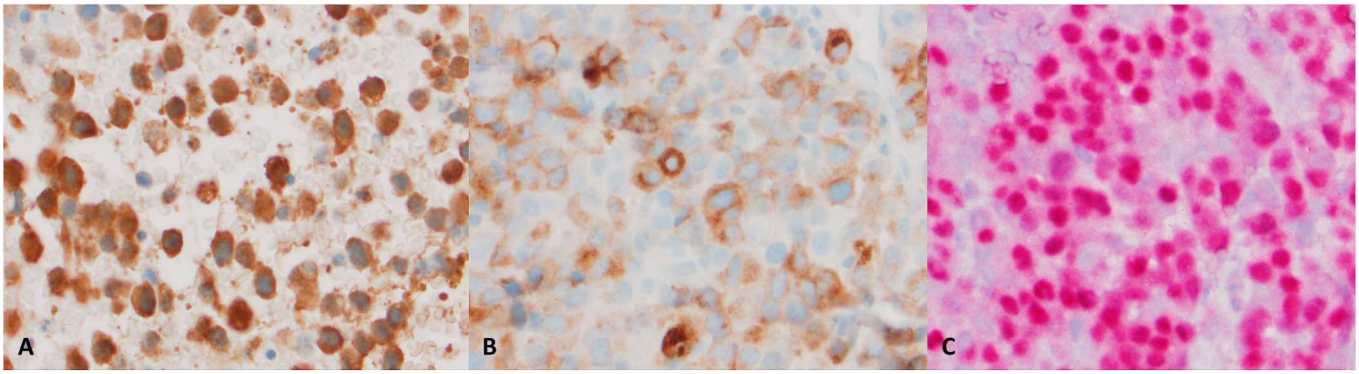

FIGURE 3. Immunohistochemical findings confirmed this to be malignant melanoma with strong diffuse positive staining for S100 (×400, A), Mart-1 (×400, B), and Sox10 (×400, C).

Although donor-related malignancy is a rare complication of transplantation, malignant melanoma is one of the most commonly reported donor-derived malignancies. If inadvertently transmitted to a recipient, melanoma may have one of the highest transmission rates and associated mortalities.[10] Most of the literature with regard to donor-related malignancies is derived from kidney transplant patients. In 18 kidney transplant patients who acquired donor-derived melanoma, 72% had advanced stage disease at the time of diagnosis and only 28% survived after 30 months.[11] Two additional studies evaluated 13 donors with a history of melanoma who provided organs to 28 recipients.[10,12] At the time of organ procurement, all donors were deemed free of melanoma and later found (or presumed) to have melanoma. In 6 of the 10 donors, the cause of death was misdiagnosed as a primary brain tumor or cerebral hemorrhage and later, on autopsy, found to be cerebral metastasis from melanoma. Melanoma transmission occurred in 21 recipients of whom 13 died of metastatic disease.

The mechanism of transmission of melanoma from the donor to recipient is unknown. There are reports that describe recipients with melanoma isolated to the allograft alone.[13,14] This finding supports the hypothesis that the allograft contains micrometastases that escape dormancy in the immunosuppressed environment. The biological behavior of melanoma is complex, and even 32% of stage I melanomas can have circulating cells.[15] Transmission of melanoma has been reported at 16, 32, and 35 years after curative resection in individual cases.[14,16–18]

The current recommendation for treatment of donor-related melanoma transmission is cessation of immunosuppression to allow rejection of the allograft and transplanted melanoma cells. After rejection has been established, the donor organ is removed. Some patients are cured by cessation of immunosuppression and organ explantation alone.[14,19,20] However, this approach does not always result in complete destruction of the tumor, and many may require additional therapy.[21]

Cutaneous melanoma metastasis to the eye is very rare. When melanoma does metastasize to the eye, it most commonly affects the uveal tract, retina, and the vitreous. Metastasis to the anterior segment, in particular to the conjunctiva and to the anterior chamber, is rarely observed.[22–27] A literature review revealed only literature on cutaneous melanoma (or no specification in the article) transmitted through donor-related transmission of malignancy (ie, no reports of uveal or conjunctival melanoma transmitted to a solid organ transplantation recipient).

Our patient developed melanoma cells within the KLAL segments and her native conjunctiva, which

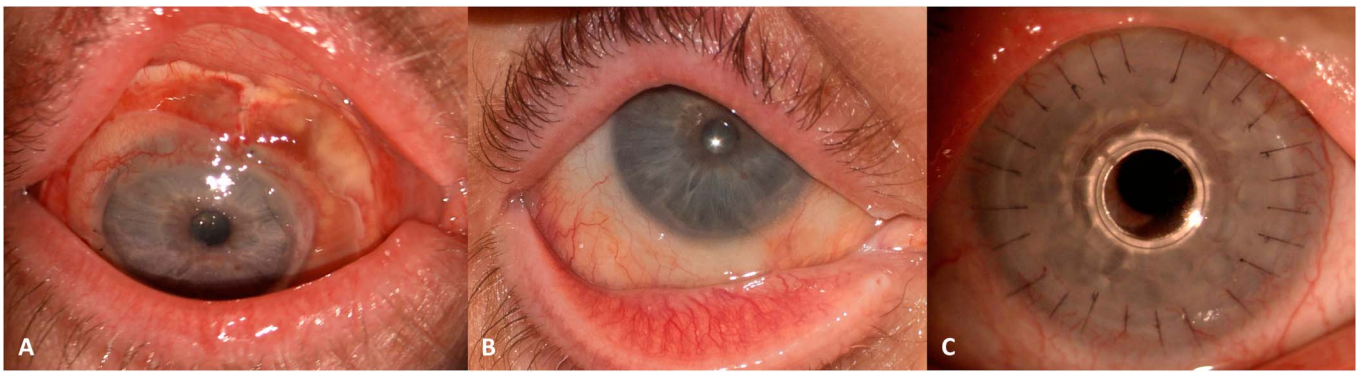

FIGURE 4. Slit-lamp photograph of the KLAL in our patient demonstrating a dramatic reduction in the tumor load within 1 week of stopping systemic immunosuppression (A, B). Slit-lamp photograph demonstrating a successful Boston type 1 keratoprosthesis performed 6 months after removal of the KLAL segments (C).

completely resolved after cessation of immunosuppression and removal of the donor KLAL. In the setting of a donor with known metastatic melanoma and development of melanoma essentially confined to the donor anatomical location, it is doubtful that this would represent a host-derived de novo melanoma that had metastasized. Currently, there is one other report of donor-related malignancy from ocular tissue donation; this involved a case of local transmission of invasive lobular breast carcinoma from a donor to a recipient in a KLAL.[28] Here, the KLAL tissue harbored donor-derived tumor cells for more than 4 years after surgery even after systemic immunosuppression was discontinued.[28] There are also 2 cases in which donated ocular tissue revealed malignant cells. Campanelli et al deferred using cornea graft tissue when the scleral rim revealed diffuse melanosis. Pathology results confirmed melanotic cells within the corneoscleral limbus and avascular cornea.[29] Yao et al[30] reported a case in which a corneal lamellar graft was replaced as a precaution after metastatic cholangiocarcinoma reaching the limbus was detected on the remaining corneoscleral rim.

Unlike the previous Eye Bank Association of America (EBAA) guidelines, the European guidelines differentiate vascular tissue donation from avascular tissue donation and have restrictions on donors with a history of malignancy for vascularized tissue donations (European Eye Bank Minimal Medical Standards, http://www.europeaneyebanks.org/files/EEBA_Minimum_Medical_Standards_Rev_2_-_2015Final.pdf, accessed May 23, 2016). Previous EBAA standards disqualified tissue only from donors with a history of leukemia, lymphoma, adenocarcinoma of the eye, retinoblastoma, and anterior segment tumors. After this case, we have changed the guidelines at our institution and no longer accept vascular ocular tissue from donors with a history of malignancy. As of June 2016, the EBAA guidelines were amended and now state that a history of melanoma (with or without metastasis) or a solid, cancerous, nonmelanoma tumor with metastasis is contraindicated for scleral tissue and KLAL donation. A history of melanoma with known metastatic disease is a contraindication for all ocular donors (EBAA Major Guidance and Standards Changes, http://eyebankingjournal.org/wp-content/uploads/2016/08/EBAA-Major-Guidance-and-Standards-Changes.pdf, accessed February 12, 2017).

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