

# Donors with Melanoma History: The Risk to Ocular Tissue Recipients

Jennifer Y. Li, MD<sup>1</sup>

## ABSTRACT

**Summary:** A case of donor-to-recipient melanoma transmission from keratolimbal allograft tissue has recently been reported to the Eye Bank Association of America. In light of this potential life-threatening adverse event, this article reviews the literature on the topic of donor-to-recipient tumor transmission both in the context of ocular tissue transplantation and solid organ transplantation specifically as it pertains to donors with a history of malignant melanoma.

**Keywords:** Melanoma; corneal transplantation; keratolimbal allograft; donor-recipient transmission

In early February of 2016, an urgent session of the Eye Bank Association of America (EBAA) Medical Advisory Board (MAB) met to discuss a potentially life-threatening adverse event from a keratolimbal allograft (KLAL). The donor had a history of malignant melanoma, and the recipient subsequently developed a malignant melanoma in the operative eye within two months of surgery.<sup>1</sup> Although formal testing to confirm the donor to recipient transmission was pending at the time of the MAB session, all clinical evidence suggested that the adverse event was directly related to the donor tissue. After reviewing this case, a unanimous consensus of the MAB placed a moratorium on ocular tissue from: 1) donors with any history of melanoma may not be released for any surgical use, and 2) donors with any history of metastatic solid tumors may not be released for surgical use of vascular components, such as conjunctiva or keratolimbal tissue.<sup>1</sup> These restrictions were effective immediately and remain in effect until the EBAA Fall Meeting on October 13, 2016. A subcommittee was created in order to further analyze the risks of tumor transmission and to propose any appropriate changes to the medical standards of the Eye Bank Association of America (EBAA).<sup>1</sup>

This appears to be the first reported case of ocular donor to recipient malignant melanoma transmission in the United

States. Prior to this adverse event and the above mentioned moratorium on donor tissue from melanoma and metastatic solid tumors, the only oncologic contraindications to transplant in the EBAA medical standards were the following:<sup>2</sup>

1. intrinsic eye disease;
  - a. retinoblastoma;
  - b. malignant tumors of the anterior ocular segment or known adenocarcinoma in the eye of primary or metastatic origin;
2. active leukemias;
3. active disseminated lymphomas.

The purpose of this article is to review briefly the literature addressing the concerns of melanoma and ocular donor tissue and to discuss the implications that it may have on ocular tissue recipients.

## Incidence of Melanoma

The incidence of melanoma has been gradually increasing over the past 30 years.<sup>3-5</sup> Melanomas are classified as melanomas in situ, those limited to the epidermis, and invasive or malignant melanomas, those that have invaded the dermis.<sup>3</sup> Including both melanoma in situ and invasive melanoma together, the incidence of melanoma been increasing by 2.6% annually. In 2014 alone, over 76,000 people in the United States were diagnosed with melanoma making it the 5th and 6th most common new cancer diagnosis in men and women respectively.<sup>4</sup> It also accounted for just under 2% of all cancer-related deaths in the United States (approximately 9700 deaths).<sup>4</sup>

## Risk of Systemic Metastases of Malignant Melanoma

Although the incidence of melanoma appears to be increasing, earlier diagnosis and initiation of treatment appear to have helped to improve 5-year survival rates from 81.8% in 1975 to 92.8% in 2006.<sup>4</sup> Despite these improvements,

**Author Affiliations:** <sup>1</sup>Associate Professor of Ophthalmology, University of California, Davis

malignant melanoma still carries a higher 5-year mortality than the general population.<sup>3</sup> It is among the leading causes of death from a cutaneous malignancy.<sup>6</sup> Five percent of melanomas are stage IV disease with distant metastases and a 5-year survival rate of less than 25%.<sup>6</sup>

The most common locations for metastasis are to the lymph nodes, skin and subcutaneous tissues.<sup>6</sup> Other common sites of metastasis include lung, liver, brain and bone.<sup>6</sup> The eye and orbit are actually uncommon sites for metastatic cutaneous melanoma.<sup>6,7</sup> Cutaneous melanoma may account for less than 5% of all metastatic disease to the eye and orbit.<sup>6,8-10</sup>

Interestingly, circulating tumor cells (CTC) have also been detected in patients with all stages of melanoma.<sup>11</sup> Up to 32% of patients with stage I melanoma had a positive CTC status.<sup>11</sup> Although CTC status cannot yet be used as a prognostic indicator clinically and its biological significance is yet to be determined,<sup>11</sup> it does point to the ability and frequency for solid tumors to shed tumor cells into the peripheral bloodstream which presumably allows for distant spread of the disease.

### **Malignant Melanoma Recurrence**

Among the major challenges with malignant melanoma is the potential for disease recurrence years after initial treatment.<sup>12-17</sup> Tahery et al reported a case of malignant melanoma recurring as late as 35 years after initial diagnosis and treatment.<sup>12</sup> The incidence of late recurrence (i.e. >10 years “disease-free” interval) ranges from approximately 1-7%.<sup>13,14</sup> In a series of 20 patients reported by Tsao et al., they estimated a minimum rate of ultra-late recurrence (i.e. ≥15 years after initial diagnosis) of 2.0% and found that the most common type of recurrence was distant metastasis (55% of cases).<sup>15</sup>

In a study of 168 late recurrences of malignant melanoma by Crowley et al., they found that the majority of patients with late recurrences had Clark’s level III or level IV lesions at the time of diagnosis.<sup>16</sup> However, patients with all levels of malignant melanoma had documented late recurrence.<sup>16</sup> Similarly, although the majority of patients had lesions of intermediate thickness (1.0 to 3.0mm), cutaneous melanomas as thin as 0.34mm had recurrences.<sup>13,16</sup>

### **Malignant Melanoma and Ocular Metastases**

As previously discussed, cutaneous melanoma has been known to metastasize to the ocular structures. Most commonly, malignant melanoma metastatic disease manifests in the eye with masses involving the uveal tract. More rarely, the retina, vitreous, anterior chamber and conjunctiva may be involved.<sup>7,18,19</sup> Typically, patients will have a history,

however remote, of cutaneous melanoma, but cutaneous melanoma presenting initially as intraocular metastases has been reported in the literature.<sup>10,20</sup>

Clinically, patients with metastatic disease to the eye may present with variable ocular symptoms ranging from floaters and hazy vision to pain and proptosis.<sup>7,10,20</sup> Some patients may even be completely asymptomatic.<sup>21</sup>

Another concerning characteristic of malignant melanoma for the purpose of addressing issues surrounding transplantation and donor transmission of disease is the potential for micrometastases, which may also be clinically asymptomatic.<sup>22</sup> In a series of 15 consecutive patients with metastatic cutaneous malignant melanoma by Fishman et al., five patients demonstrated evidence of intraocular metastasis.<sup>22</sup> Of these five patients, three had choroidal metastasis. One eye had infiltration of the retina, and the fifth eye had multiple tumor nodules originating from emboli in the peripheral retinal vessels.<sup>22</sup> Of note, all of the patients were undergoing treatment for disseminated melanoma, and there was no difference in age, duration of illness or primary site between patients with and those without ocular metastases.<sup>22</sup> The study by Fishman et al. demonstrated a much higher rate of ocular metastases from cutaneous melanoma than previously reported.<sup>22</sup> They speculate that the actual incidence of ocular metastases may be even higher since only a limited number of histologic sections were available for examination in these patients. Additionally, none of the patients were examined by an ophthalmologist during their illness, but given the nature of their histopathologic findings, there may not have been any observable clinical findings.<sup>22</sup>

### **Potential for Donor Tumor Transmission: Solid Organs**

The potential for donor-to-recipient transmission of melanoma in solid organ transplants is a rare but known risk of transplantation.<sup>13,23-26</sup> Malignant melanoma is, unfortunately, one of the most commonly reported donor-derived malignancies with one of the highest rates of associated mortality.<sup>23</sup> A past history of melanoma remains a strong contraindication to solid organ donation regardless of the duration of remission from initial surgical resection. Bajaj et al. has reported a case of donor melanoma transmission to a lung transplant recipient after 32 years of being “disease-free” following surgical excision of melanoma.<sup>13</sup>

The source for the tumor is thought to be from either micrometastases within the transplanted organ, or from circulating tumor cells within in the organ.<sup>23-25</sup> It is not well-understood how metastatic melanoma is able to remain dormant for years at distant sites. It is thought that

anti-tumor immunologic responses suppress the tumor, and that transplantation, with subsequent immunosuppression of the recipient, allows for recurrence and spread of the previously dormant melanoma.<sup>13,26</sup> In 2004, Buell et al. reported on 124 cases of confirmed donor cancer transmission from 296 donors with known or incidental malignancies.<sup>27</sup> They found that melanoma had a high tumor transmission rate of 74% with a 58% rate of mortality, second only to choriocarcinoma.<sup>27</sup>

### Potential for Donor Tumor Transmission: Ocular Tissue

While the risk of donor-to-recipient transmission of melanoma in solid organ transplants is well documented, the same cannot be said for ocular tissue transplants. Until now, donors with systemic solid tumor malignancies have been eligible for ocular tissue transplantation. These donors may constitute upwards of 30 to 40 percent of the donor pool.<sup>28-30</sup>

Several groups have looked at the risks of donor-to-recipient tumor transmission through corneal transplantation and found that the risk is very low.<sup>28-31</sup> Wagoner et al. performed a long-term retrospective analysis of 73 patients who corneal donor material from donors who died of various systemic malignancies.<sup>28</sup> They found no increased incidence of malignancy or earlier mortality in the recipient population and no patient developed local tumor growth.<sup>28</sup>

Similarly, López-Navidad et al. evaluated outcomes from 204 corneal donors with active malignancy or a history of malignancy.<sup>30</sup> In their donors, 86.8% had solid tumor malignancy and 13.2% had hematological cancer. At the time of donor death, 94.7% had active malignancy and 64% had metastatic spread of their primary tumor. They were able to follow 325 recipients of corneas from donors with cancer for an average of 64.1 months and had no cases of donor-to-recipient tumor transmission. They also performed histopathological evaluation of the remaining corneoscleral rim after the donor button was removed and transplanted. They found no gross masses in the eye or cellular infiltration of the anterior chamber structures in any of the 408 eyes evaluated. By histology, two eyes (0.5%) from two donors were found to have micrometastases. Of these, one was a single focal infiltration of malignant cells in the choroid from a donor with breast adenocarcinoma. The second donor had chronic myeloid leukemia and leukemic infiltrates primarily in the scleral and episclera. Neither of the corneas transplanted from these two eyes with micrometastases resulted in donor-to-recipient tumor transmission with greater than 6 years of follow-up.

In the literature, there are only two reported cases of tumor transmission through corneal transplantation, neither relat-

ed to malignant melanoma.<sup>32,33</sup> One case described in 1939 involved a primary retinoblastoma,<sup>32</sup> and the second case was from a donor who upon further review, had probable bilateral choroidal metastases prior to death from disseminated adenocarcinoma.<sup>33</sup>

Finally, Campanelli et al. reported a case of cutaneous melanoma metastasis to ocular donor tissue presumably through hematogenous spread.<sup>34</sup> In their case, the corneal tissue did not show signs of disease or neovascularization and was considered suitable for transplantation based on standard criteria. However, they performed further histologic analysis given the aggressive nature of the donor's metastatic melanoma and found atypical cells positive for the melanocytic differentiation marker S100 in the avascular paracentral cornea, in the sclerocorneal limbus, and in the sclera. In light of their findings, the authors subsequently contacted 7 recipients who had received other corneas from donors who died of metastatic cutaneous melanoma. They found that none had developed cancer up to 3 years after corneal transplantation.<sup>34</sup>

The studies by Campanelli et al. and Fishman et al. demonstrating ocular micrometastases from cutaneous melanoma raises some concern regarding the risks of donor tumor transmission.<sup>22,34</sup> However, prior to this current reported case of KLAL donor-to-recipient melanoma transmission,<sup>1</sup> there is little evidence clinically to support the risk of donor-to-recipient tumor transmission in the context of corneal transplantation.<sup>28-31,34</sup> There appears to be very low risk of donor-recipient tumor transmission with corneal tissue. The reason for this may be multi-factorial. The avascular nature of corneal tissue may be one reason why donor-recipient tumor transmission is rare. Additionally, unlike with solid organ transplants, the lack of systemic immunosuppression in corneal transplant recipients may prevent the re-activation of potentially dormant malignant cells. With KLAL, however, these potentially protective factors are no longer present. KLAL tissue is vascular unlike corneal tissue and is transplanted into a highly vascular region of the eye. Moreover, patients undergoing KLAL surgery require prolonged systemic immunosuppression to improve the likelihood of success.<sup>35,36</sup> Thus, these recipients in many ways, are more similar to solid organ recipients than corneal transplantation recipients.

### CONCLUSIONS

Moving forward, the eye banking community has many difficult questions to answer, and decisions that will need to be made regarding the eligibility of ocular donors with malignancies and in particular, malignant melanoma. Although we are always driven by data and not anecdotal evidence,

the reality is that these cases of donor-recipient tumor transmission are rare, and it would be virtually impossible to study this in a prospective manner. Excluding all malignancies from the donor pool would be rash and potentially devastating to the donor pool and our ability to meet the current level of demands for ocular tissue. However, continuing with our current standards that allow for virtually all donors with malignancies (exceptive leukemia and lymphoma, retinoblastoma and anterior segment tumors) for all types of ocular donor tissue also seems unwise.

With the many advances that we have made over the past decade in anterior segment transplantation and the use of ocular donor tissue, we will need to evaluate carefully the risks of different malignancies on the various types of ocular tissue available for transplantation. The risks of donor-recipient tumor transmission for vascular and avascular tissue will likely need to be evaluated separately. The risks of donors with a history of malignant melanoma may need to be evaluated apart from other tumors and malignancies. The burden is on the eye banking community to continue to address these concerns and to continue improving the safety of all ocular donor tissue. As stated in the mission of the EBAA, we must continue to be champions for the restoration of sight, and ultimately, we must continue to be champions for the well being of the patients that we serve.

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