Article published online: 2021-08-09

CASE REPORT

Donor-transmitted melanoma after limbal stem cell transplantation

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Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/2231-0770.203609

Quick Response Code:

ABSTRACT

Limbal Stem Cells are a unique cell line located at the corneal limbus. They are responsible for regenerating and restoring corneal epithelial layers. Limbal stem cell transplantation is a promising technique that has been used to treat several hereditary and acquired corneal diseases. Cornea tissue lack vascularity. Hence, there were no special restrictions on collecting ocular tissues from donors with a diagnosis of metastatic melanoma. We are reporting a case of a patient who developed an ocular melanoma after she had limbal stem cell transplantation from a donor with history of melanoma. After this case, Eye Bank Association of America updated the donor criteria to exclude donors with any history of melanoma.

Key words: Donor-transmitted melanoma, limbal stem cell transplant, transplant-related malignancy

INTRODUCTION

Limbal stem cell transplant (LSCT) represents a promising treatment for many ocular conditions. In general, posttransplant immunosuppression status predisposes to malignancy. We are reporting a case of donor-derived melanoma following LSCT. Before this case, Eye Bank Association of America accepted limbal stem cell donors with active malignancies except for leukemia, lymphoma, myeloma, retinoblastoma, and tumors of the anterior segment of the eye. To the best of our knowledge, there were no previous reports in the literature of LSCT with a similar complication.

CASE REPORT

Patient is a 56-year-old Caucasian female, with a history of corneal dystrophy that progressed to bilateral limbal stem cell deficiency (LSCD). The patient received a right eye LSCT from a cadaveric donor. The LSCT was initially complicated with keratoconjunctivitis, so she was treated with systemic and topical antibiotics. To prevent graft rejection, systemic immunosuppressive therapy (prednisone, tacrolimus, and mycophenolate mofetil), as well as topical ocular immunosuppressive therapy (prednisolone acetate, cyclosporine, and difluprednate), were initiated.

Ten weeks after the transplantation, she presented to her ophthalmologist with a complaint of a sudden decrease in vision acuity of the right eye. The eye exam revealed what appeared to be right eye subconjunctival hemorrhage. A following orbital computerized axial tomography scan revealed a right intraorbital soft tissue mass measuring 1.8 cm (horizontal) × 1.5 cm (vertical), with preseptal thickening [Figure 1]. There were no intraconal or intraocular masses. The management options were discussed with the patient, and she declined eye enucleation surgery and insisted on preserving her eyeball. The patient did agree to tumor resection, which was performed with partial tarsorrhaphy. Furthermore, the immunosuppression therapy was held.

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Cite this article as: Alsara A, Rafi M. Donor-transmitted melanoma after limbal stem cell transplantation. Avicenna J Med 2017;7:75-7.

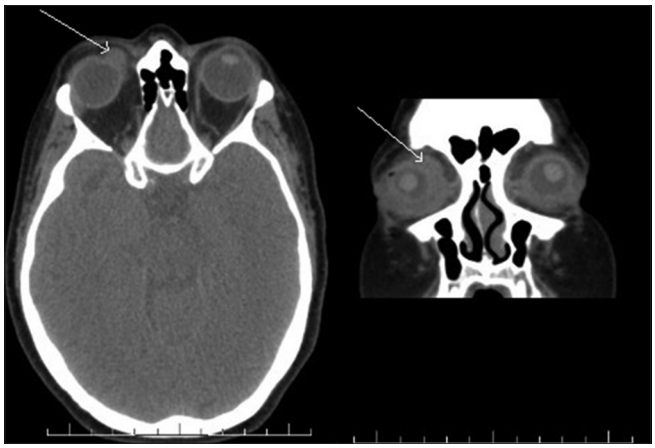

Figure 1: Orbital computerized axial tomography scan illustrate intraorbital mass: Axial window (left) coronal window (right)

The biopsy pathological evaluation was consistent with a malignant neoplasm. In addition, immunostaining was strongly positive for S100, melanoma antigen recognized by T cell (cytoplasm), and SOX-10 (nuclear). The tumor cells were negative for pankeratin, p40, and leukocyte common antigen (CD45). The histologic and immunohistochemical findings were characteristic of a malignant melanoma and ruled out both undifferentiated carcinoma and lymphoma.

At this point, the patient was referred to a medical oncologist for further management. A positron emission tomography scan ruled out any undifferentiated, occult primary neoplasm. A review of the donor medical records revealed that he died due to malignant melanoma. The histopathological evaluation of BRAF mutation in the melanoma cells was negative in both the patient and the deceased donor.

The patient was also treated with topical mitomycin C (MMC) chemotherapy and had a successful keratoprosthesis to improve her vision. She is now following up with an ocular oncologist for further management with possible radiation.

DISCUSSION

The cornea is an avascular tissue covered anteriorly by a multilayer stratified, nonkeratinized epithelium. This epithelium is constantly regenerated by limbal stem cells, a unique cell population located in the basal epithelial layer of the corneal limbus (the corneo-conjunctival junction).[1] The corneal stroma is an avascular collagenous layer with a very poor propensity for neoangiogenesis. Hence, before this case, there were no special restrictions on obtaining ocular tissues for transplantation from donors with metastatic melanoma. The Eye Bank Association of America accepted ocular tissue from donors with active malignant tumors except for active leukemia, lymphoma, myeloma, retinoblastoma, and tumors of the anterior segment of the eye.[2]

Corneal limbal stem cells may be destroyed or become dysfunctional as a result of several hereditary and acquired conditions. LSCD can lead to corneal opacity and vascularization, with consequent vision impairment or blindness. When limbal stem cells are completely depleted, then any successful treatment must include the introduction of new stem cells. This treatment is called LSCT. There are four LSCT procedures that have been developed: conjunctival-limbal autologous transplantation; living-related conjunctival-limbal allogeneic transplantation; keratolimbal allogeneic transplantation; and *ex vivo* expansion of LSCT.[3]

Reported long-term complications of LSCT include epithelial rejection; microbial keratitis; corneal necrosis; and corneal ulceration. These complications can usually be treated with antibiotics. However, failure of treatment may result in graft rejection.[3] In general, allograft transplantation has the risk of rejection even in human leukocyte antigen-matched recipients. Therefore, all allograft transplants require prolonged systemic immunosuppression to decrease eye inflammation and prevent allograft rejection.[4]

Topical (ophthalmic) immunosuppressants alone are usually insufficient in controlling allograft rejection. Treatment regimens combining both topical and systemic immunosuppressive are usually preferred.[1,5]

However, one of the adverse effects of the long-term immunosuppressive status after organ transplantation is a malignancy, which represents a major contributor to morbidity and mortality in the organ-recipient population.[6] Malignancies might arise after different types of transplantation: solid organ transplantation, bone marrow transplantation, and hematopoietic stem cell transplantation.[7,8]

These malignancies develop in one of three contexts:

1. *De novo* malignancy in the immunosuppressed recipient is the predominant mechanism. Nonmelanoma skin cancer is the most common malignancy to develop following solid organ transplantation[9]
2. Recurrence of treated pretransplant malignancy is less frequent. The highest recurrence rate was for breast cancer, symptomatic renal cell cancer, sarcoma, bladder cancer, and multiple myeloma.[10] There is no evidence of increased risk for melanoma in organ transplant population compared to the general population[7]

3. Unintended transmission of malignant cells from a donor is relatively rare.[9] Birkeland and Storm estimated a 1.3% risk of having a donor with previously undetected malignancy and a risk of 0.2% for a recipient to develop a transmitted malignancy.[11] Renal cell carcinoma is the most commonly transmitted cancer originating in the donor organ, while malignant melanoma is the most common transmitted cancer with distant metastases.[6,12]

To the best of our knowledge, this case of donor-transmitted malignant melanoma following LSCT is the first to be reported.

Donor transmission of melanoma can be explained by tumor cell dormancy. Melanoma cells are considered "dormant" when a balance is achieved between active proliferation and apoptosis in micrometastases. Dormancy also occurs in the absence of proliferation and apoptosis in solitary tumor cells. Melanoma cells, whether micrometastases or solitary tumor cells, can stay dormant for years, residing in the organ parenchyma or circulating within the vasculature. However, they may "escape" the state of dormancy in immunosuppression settings as with posttransplant conditions.[7]

Recommendations for management of donor-transmitted melanoma include withdrawal of immunosuppression therapy, which potentially prompts rejection of the tumor cells. Removal of the allograft may also be considered.[13,14] Because the complete removal of malignant cells is not always possible, some authors suggest adding adjuvant chemotherapy to eliminate residual tumor cells.[15] In particular, topical chemotherapy with MMC has been established as a good adjuvant therapy option for various conjunctival tumors. MMC is an alkylating antibiotic that affects all phases of the cell cycle.[16] It has good tolerability with mild side effects, including transient keratoconjunctivitis and decreased conjunctival pigmentation.[17] Additional randomized trials are needed for the final evaluation of MMC therapy for ocular melanoma.[18]

CONCLUSION

Posttransplant malignancy is a major limitation to successful transplantation and may increase transplant-related morbidity and mortality. Immunosuppression status following transplantation predisposes to malignancy. No previous case of donor-transmitted malignancy following LSCT has been reported yet. Management of donor-transmitted melanoma includes withdrawal of immunosuppression, tumor excision, and adjuvant therapy. Prevention is essential and emphasizes the importance of careful cancer screening for stem cell donors. After reporting this case to the Eye Bank Association of America, which previously accepted patients with an active or remote history of melanoma, the criteria for ocular tissue donors have been reviewed. New exclusionary criterion was added, stating that ocular tissue from donors with any history of melanoma may not be released for any surgical use.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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