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Periocular Skin Cancer in Solid Organ Transplant Recipients

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Purpose: To determine the proportion of solid organ transplant recipients developing periocular nonmelanoma skin cancer and to describe the morbidity of these cancers in transplant recipients.

Design: Cohort study.

Participants: Consecutive patients undergoing solid organ transplantation at the Cleveland Clinic between 1990 and 2008.

Methods: The charts of all patients receiving a solid organ transplant from 1990–2008 evaluated in the dermatology department for a subsequent biopsy-proven head and neck malignancy through April 2015 were reviewed. Patients with a periocular region nonmelanoma skin cancer (NMSC) or a nonperiocular NMSC causing a complication requiring eyelid surgery were included. Charts were reviewed for demographic data; transplant date, type, and source; immunosuppressive agents received at diagnosis; and type of NMSC, number of nonperiocular NMSCs, ophthalmologic findings, and periocular sequelae after the repair.

Main Outcome Measures: Primary outcome measures included the type, location, final defect size, tumor-node-metastasis classification, presence of perineural invasion, and reconstruction technique(s) used for each periocular NMSC. Secondary outcome measures included the type and treatment of ocular sequelae due to nonperiocular facial NMSC.

Results: A total of 3489 patients underwent solid organ transplantation between 1990 and 2008. Of these, 420 patients were evaluated in the dermatology clinic for biopsy-proven NMSC of the head and neck during the study period, and 11 patients (15 malignancies) met inclusion criteria. Nine patients developed 12 periocular malignancies and 3 patients required eyelid surgery for facial malignancies outside the periocular zone. All 11 patients developed a squamous cell carcinoma (14 malignancies), and 1 patient (1 malignancy) also developed a periocular basal cell carcinoma. There was orbital invasion in 4 cases and paranasal and/or cavernous sinus invasion in 3 cases. Two patients underwent exenteration. Seven cases required reconstruction with a free flap or graft. Periocular sequelae included lower eyelid ectropion (6 malignancies), dry eye and/or exposure symptoms (8 malignancies), unilateral vision loss (3 malignancies), and facial nerve paresis (5 malignancies).

Conclusions: Squamous cell carcinoma affecting the periocular region represents a risk of solid organ transplantation and may produce significant ocular morbidity, including the need for major eyelid reconstruction, globe loss, and disfiguring surgery. *Ophthalmology 2015;■:1–6 © 2015 by the American Academy of Ophthalmology.*

Nonmelanoma skin cancer (NMSC) has emerged as a significant complication of solid organ transplantation and consequent immunosuppression. More than one half of transplant recipients go on to have NMSC, and a second NMSC develops in up to 80% of these patients.[1–6] Squamous cell carcinoma and basal cell carcinoma account for 95% of all skin cancers in this population,[7,8] and transplant recipients incur an increased risk for these malignancies of up to 250-fold and 10-fold, respectively.[2,7,9,10] Although the incidence of eyelid squamous cell carcinoma in a general population has been described as 1.37 per 100 000 per year, the incidence of eyelid NMSC in transplant recipients remains unknown.[11]

Transplant immunosuppressants increase the incidence of NMSC via decreased immunosurveillance and other mechanisms; the exact mechanisms differ between immunosuppressants.[2,10,12] Purine analogs promote development of NMSC resulting from photosensitization and oxidative DNA damage by mutagenic metabolites.[2,6,7,12] Calcineurin inhibitors promote tumor formation through effects independent of immunosuppression, by increasing transforming growth factor β and vascular endothelial growth factor levels.[7] Tacrolimus and mycophenolate mofetil compromise the proper response to ultraviolet B-induced DNA damage in keratinocytes by inhibiting ultraviolet B-induced apoptosis and ultraviolet B-induced checkpoint signaling.[13]

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The risk of skin cancer developing in transplant recipients increases with the duration and dose of immunosuppression, with regimens involving more than 2 drugs, and with specific immunosuppressive drugs.[2,5,7–9,12,14–18] Additional risk factors include exposure to ultraviolet radiation, a first NMSC, the type of organ received, genetic variations, infection with human papilloma virus or human herpes virus (HHV), and tobacco and alcohol use.[3,17,19–22] The increasing survival and number of patients receiving organ transplants over the last 30 years has increased the likelihood of NMSC and total tumor burden in this population.[2,9,18]

Even in patients with intact immune systems, periocular cutaneous malignancies typically present with few signs or symptoms, often delaying diagnosis.[23,24] Cutaneous eyelid malignancies may result in globe exposure, nerve damage, vision loss, globe loss, or loss of life.[9,23,24] Because transplant recipients experience skin cancers at a younger age, with increased incidence and aggressiveness,[2] periocular lesions may produce a particularly significant impact on quality of life. We sought to characterize the proportion and morbidity of NMSC affecting the periocular region in solid organ transplant recipients.

Methods

A database of consecutive patients undergoing solid organ transplantation at the Cleveland Clinic between 1990 and 2008 was used to identify all charts with a dermatology clinic visit for a subsequent biopsy-proven head and neck malignancy developing through April 2015. The following criteria were used for inclusion: NMSC within the periocular region or skin cancer outside the periocular region causing a condition necessitating eyelid surgery. The periocular region was defined as any aspect of the defect within the orbital rim. Institutional review board approval was obtained for this study, and this research adhered to the tenets of the Declaration of Helsinki.

Charts were reviewed for gender; race; age at diagnosis of facial or periocular malignancy; age at transplant; transplant date, type, and source; immunosuppressive agents received at diagnosis; type of periocular malignancy; number of nonperiocular skin cancers; whether visual acuity changed because of malignancy treatment; and periocular morbidity from the malignancy. Periocular morbidity was defined as loss of periocular or orbital tissue, vision loss, nerve damage, or extension within the orbit, adjacent sinuses, or both. Morbidity was divided into orbital invasion, orbital exenteration, sinus invasion, periocular reconstruction requiring a microvascular free flap or a free graft, eyelid insufficiency or ectropion, vision loss, and facial nerve paresis.

Charts also were reviewed for tumor type, tumor location, and final defect size, as well as for the reconstruction technique(s) used. Eyelid cancers were staged according to the eyelid carcinoma classification system from the American Joint Committee on Cancer, 7th edition.[25]

Results

A total of 3649 solid organ transplantations were performed on 3489 patients at the Cleveland Clinic between January 1999 and January 2008. There were 1243 (34%) kidney, 800 (22%) liver, 682 (19%) heart, 514 (14%) lung, 94 (6%) pancreas, 4 (0.1%) intestine, and 152 (4%) combined transplant recipients. Of these patients, 420 patients (12%) were evaluated in the Cleveland Clinic Department of Dermatology for a head and neck NMCM during the study period. There were 344 (82%) men and 76 (18%) women with head and neck NMSC after transplantation who had undergone lung (122 patients [29%]), heart (108 patients [26%]), kidney (97 patients [23%]), liver (67 patients [16%]), or combined (26 patients [6%]) transplants. Four hundred fifteen patients were white, 2 patients were black, and 3 patients were of unknown race with head and neck NMSC after transplantation.

Table 1. Organ Type and Source for Transplant Recipients

Patient	Transplant Type	Age at Transplant (yrs)	Race/Ethnicity	Organ Source
1	Lung	58	White	Cadaveric
2	Liver	67	White	Expanded
3	Lung	57	White	Cadaveric
4	Kidney	62	White	Living related
5	Lung	60	White	Cadaveric
6	Kidney	63	White	Cadaveric
7	Lung	32	White	Cadaveric
8	Kidney	51	White	Cadaveric
9	Liver	52	White	Cadaveric
10	Kidney	25	White	Living related
11	Kidney	54	White	Cadaveric

Eleven patients met inclusion criteria, and all were white. Eight were men and 3 were women. The type of transplant included kidney (5 patients [45%]), lung (4 patients [36%]), and liver (2 patients [18%]). The average time from solid organ transplantation to first eyelid malignancy was 7.4 years (range, 2–16 years). Table 1 summarizes transplant recipient demographic data.

A total of 51 transplant recipients with a head and neck malignancy in the study period were evaluated in the Department of Ophthalmology, including all 11 patients requiring periocular surgery because of a cutaneous neoplasm. The remainder of the patients evaluated in the Department of Ophthalmology did not show evidence of an ocular sign or symptom resulting from the head and neck neoplasm(s). All 11 patients underwent examination and eyelid reconstruction by 1 author (J.D.P.).

Nine patients demonstrated 12 primary periocular malignancies affecting 11 eyes (6 right eyes and 5 left eyes). The first encounter with all 12 periocular malignancies was at their primary identification. Three patients experienced complications from 4 nonperiocular facial malignancies that affected 4 eyes (1 right eye and 3 left eyes). One eye was affected by both a periocular malignancy and a nonperiocular facial malignancy. The proportion of all transplant patients with a biopsy-proven cutaneous malignancy requiring surgery in the periocular region was 0.32%, and the proportion of transplant recipients with a head and neck malignancy requiring surgery in the periocular region was 2.6%.

In the 9 patients with 12 primary periocular malignancies, 9 patients had a squamous cell carcinoma (11 malignancies) and 1 patient also had a basal cell carcinoma (1 malignancy). A discrete malignancy isolated to an eyelid occurred in 3 of 12 cases and involved only the eyelid margin in 2 of 12 cases, whereas the lesion involved skin beyond the periocular region in 9 of 12 cases. Local recurrence was noted in 6 of 12 periocular malignancies, occurring in 5 patients (patients 1, 3, 4, 6, and 8, with patient 3 demonstrating bilateral recurrence). The final defect size was at