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Melanomas in Renal Transplant Recipients: A Single-center Study

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ABSTRACT Skin cancers are the most common malignancies in renal transplant recipients, with squamous-cell and basal-cell cancers accounting for the majority of all skin cancer cases. Melanoma is relatively rare in this group of patients. From 1973 to May 2017, out of 1889 patients who received allografts at our institution, 4 developed melanoma. After the mean follow-up of 11.5 months, 2 patients died and 2 are still alive with functioning allografts. Malignancies were localized in the legs in both female patients, and in the neck and head in 1 male patient each. Compared to the general population of Croatia, renal transplant recipients from our cohort have 6.85 times higher risk for development of melanoma. Regular screenings and patient education are mandatory, especially in Mediterranean countries.

KEY WORDS: skin cancer, melanoma, renal transplantation, immunosuppression, outcome

INTRODUCTION

Skin cancers are the most common malignancies in renal transplant recipients. Squamous-cell and basal-cell cancers account for the majority of all skin cancer cases and are clearly associated with prolonged exposure to immunosuppression (1,2). Melanoma is relatively rare in this group of patients, but the risk is still 2 to 3 times higher when compared with the general population. Literature on melanoma in the renal transplant population is scarce.

Herein we report clinical characteristics of patients who developed melanoma after renal transplantation at our institution.

PATIENTS AND METHODS

This retrospective study included all renal transplant recipients who received a renal allograft at the University Hospital Centre Zagreb and developed post-transplant melanoma from 1973 to May 2017. Patients were followed by nephrologists and dermatologists. Data were retrieved from the database of the Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation, University Hospital Centre Zagreb and from medical charts and records.

The data collection included patient age and gender; dialysis vintage; immunosuppressive regimen before and after diagnosis of malignancy (induction

with basiliximab or antythymocyte globuline (ATG), maintenance with either azathioprine, prednisone, cyclosporine, everolimus, mycophenolate mofetil, or tacrolimus); rejection episodes; time from transplantation until the diagnosis of malignancy; other concurrent neoplastic problems; time of follow-up and outcome.

Before the year 2000, patients received triple maintenance immunosuppression with cyclosporine, prednisone, and azathioprine. After 2000, the majority of patients were taking cyclosporine, prednisone, and MMF, and tacrolimus instead of cyclosporine from 2009. Simulect was used for induction in all patients from 2007, and ATG in cases of second transplantation or in sensitized patients.

RESULTS

Four patients out of the 1889 renal transplant recipients developed melanoma over the observed period, resulting in a prevalence of 0.2%. There were 2 male and 2 female patients. Mean dialysis vintage was 3.25 years. One patient was treated with peritoneal dialysis, and 3 with hemodialysis. Mean age at transplantation was 57 years. Two patients received basiliximab induction followed by tacrolimus, mycophenolate, and steroid maintenance, 1 was treated with cyclosporine, mycophenolate and steroids, and 1 with cyclosporine, azathioprine, and steroids. Mean age at diagnosis of malignancy was 64.75 years (range 61-69) with median exposure to immunosuppression of 7.625 years (range 1.5-20.0). Melanomas were localized at the legs in 2 female patients and at the neck and the head in 1 patient each. All patients underwent surgical excision. Tacrolimus was switched to everolimus in 2 patients, while in 1 patient cyclosporine was omitted from the immunosuppressive protocol (she was diagnosed before the introduction of mTOR inhibitors in Croatia). A male patient (Number 3) had proteinuria, which was a contraindication for a switch from cyclosporine to everolimus. Thus, cyclosporine was discontinued and treatment continued with mycophenolate and steroids (Table 1).

Median follow-up after diagnosis of melanoma was 11.5 months. Two patients died, and 2 are still alive with functioning allografts.

DISCUSSION

There is conflicting data on the incidence of melanomas in renal transplant recipients. Some epidemiologic studies have shown that the risk of melanoma is increased after renal transplantation (3), however, a study from the Netherlands did not find increased risk for development of melanoma in this group of patients (4). The pathogenesis of these neoplasms is likely related to immune suppression after organ transplantation and subsequent viral infection (2,5). Lindelof *et al.* evaluated 5356 patients over a 24-year period, with melanoma found in 6 patients. The authors concluded that transplant patients had no increased risk for development of melanoma (6). The United States Renal Data System (USRDS) found a 2.2-fold increase in melanoma among renal transplant recipients (1). Later, Hollenbeak *et al.* also using data from USRDS (7), found 246 cases of melanoma among 89786 renal transplant recipients from 1988 and 1998. The age-adjusted incidence rate of melanoma was 55.9 cases per 100000 individuals, which is a 3.6 times greater age-adjusted standardized risk compared with the general population. The Penn Israel registry recorded 177 *de novo* patients with melanoma in their transplant population over a 27-year-period (8). Melanoma (mostly Breslow thickness >0.76 mm) was more common in men, occurred 1 to 244 months after transplantation, most on the trunk, upper limbs, head, and neck. According to data published in the Croatian National Cancer Registry for year 2014 (9), incidence of melanoma was 0.137 per 1000 citizens, which is 6.85 times lower than in our renal transplant population.

The outcomes of patients who develop melanoma after renal transplantation depends primarily on the characteristics of the malignancy. It appears that those patients with melanoma Breslow thickness <0.76 mm have a good prognosis, as in the general

Table 1. Patient characteristics

	Gender	Dialysis vintage (yr)	Age at tx	Duration of tx (yr)	Immunosuppression	Switch	Age at development of malignancy	Breslow (mm)	Location	Follow-up (mo)	Recidive	Outcome
1	F	4	61	5.0	Bas, tac, MMF, ster	everolimus	66	0.35	leg	22	No	Alive
2	M	5	59	1.5	CyA, MMF, ster		61	4.00	head	6	Meta	Exitus
3	M	2	65	4.0	Bas, tac, MMF, ster	everolimus	69	1.40	neck	7	No	Alive
4	F	2	43	20.0	CyA, Aza, ster		63	5.00	leg	11	Meta	Exitus

F: female; M: male; tx: transplantation; Bas: basiliximab; tac: tacrolimus, cyA: cyclosporine A; MMF: mycophenolate mofetil; Aza: azathioprine; ster: steroids; Meta: metastasis; yr: year; mo: month

population, while patients with Breslow thickness >0.76 mm may have increased mortality (8,10-13). Harwood *et al.* reported outcomes in 7 patients, 2 with *in situ* melanoma and 5 with invasive melanoma (14). Three patients died from metastatic disease; 2 of them with Breslow >2 mm. However, one patient developed metastases from a lentigo maligna melanoma with Breslow thickness of 0.4 mm. In a report by Dapprich *et al.* who followed 31 patients with *de novo* malignant melanoma after transplantation with Breslow thicknesses ranging from *in situ* to 6.1 mm (median, 0.75 mm), Breslow depths greater than 1.0 mm were associated with recurrences, metastasis, and death (15). Among 139991 non-Hispanic white transplants recorded in the US transplant-cancer registry data (1987-2010), the risk of invasive melanoma (n=519) was elevated 2.2 times. Risk of localized tumors was higher with azathioprine maintenance therapy. Risk of regional/distant stage tumors was the highest 4 years following transplantation and increased with the use of polyclonal antibodies. Mortality from melanoma was higher among transplant recipients than in the general population (hazard ratio 2.98) (16).

It is interesting that 2 of our patients (50%) had other malignancies associated with melanoma (papillary thyroid carcinoma and renal adenocarcinoma; submandibular gland tm). Bae *et al.* analyzed other primary cancers in 452 patients with melanoma from 1994 to 2013. They found 51 cases (11.2%) of other primary cancers, most commonly gastrointestinal, thyroid, lung, and breast cancer (17).

Immunosuppression is an important factor in development of post-transplant malignancies. mTOR inhibitors were found to decrease the incidence of malignancies in renal transplant recipients (18). Experimental models on mice demonstrated that treatment with mTOR inhibitors inhibited melanoma tumor growth (19). These results may support a switch from calcineurin-inhibitor-based- to mTOR-inhibitor-based immunosuppression after development of melanoma.

Prevention should be the primary approach in the renal transplant population. Patients should be instructed on self-examination of the skin and sun protection strategies. Dermatologic examinations should be performed on all patients at high risk, with special attention to all pigmented lesions and excisional biopsies performed on all suspicious nevi.

CONCLUSION

Melanoma is relatively rare in the renal transplant population; however, it was found to be 6.85x more common in this group when compared with the general population.

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