Melanoma in a cohort of organ transplant recipients: Experience from a dedicated transplant dermatology clinic in Victoria, Australia

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Background: There is limited information on the profile of melanomas diagnosed in a specialist transplant dermatology clinic.

Objective: To describe the incidence and characteristics of incident primary melanomas in a cohort of organ transplant recipients (OTRs) attending a specialized transplant dermatology clinic and determine the number of pigmented lesions needed to excise for every melanoma diagnosed.

Methods: A retrospective study of 327 OTRs monitored by an Australian clinic during a 10-year period.

Results: There were 11 incident melanomas diagnosed during a total follow-up of 1280 patient-years. The mean interval between the first transplant and diagnosis was 5.5 years. Only 2 melanomas were >1 mm in Breslow thickness. Seven melanomas (64%) arose de novo. A contiguous nevus was present in 4 cases. Metastatic disease did not develop in the melanoma patients during the follow-up period, and all remain alive. The needed to excise for every melanoma diagnosed ratio was 16:1.

Limitations: The crude incidence rates were age standardized, unlike the comparison rates of melanoma in the general population, and the cohort was small.

Conclusion: Most melanomas diagnosed in OTR patients attending a specialized transplant dermatology service were detected early. Our data suggest early detection may reduce the proportion of OTRs presenting with thick melanomas, thus improving prognosis and patient outcomes. A needed to excise for every melanoma diagnosed ratio of 16:1 is not unreasonable for this cohort of high-risk patients. To our knowledge, this is the first time this ratio has been calculated for a cohort of OTRs. (J Am Acad Dermatol 2020;83:773-9.)

Key words: biopsied pigmented lesions; histopathology; immunosuppression; keratinocyte cancers; melanoma; multimodal therapy; organ transplant recipients; pigmented cutaneous lesions; post-transplantation; solid organ transplantation; transplant dermatology.

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Cutaneous carcinogenesis is an important complication of solid organ transplantation.[1] In countries with high ultraviolet radiation and a susceptible population, keratinocyte cancers are the most common post-transplant malignancy in organ transplant recipients (OTRs), accounting for 27% to 37% of all de novo neoplasms.[2,3]

Melanoma incidence is also increased 3- to 5-fold compared with the general population.[4-6] Furthermore, population based-studies have shown that the prognosis of OTR diagnosed with de novo invasive melanoma is significantly worse than in the matched immunocompetent population.[7,8]

We performed a retrospective study of a dedicated transplant dermatology clinic in Victoria, Australia, during a 10-year period. Our findings suggest improved prognosis in our cohort of patients with post-transplant melanomas. We were also able to quantify the benign-to-malignant ratio of pigmented cutaneous lesions in this cohort.

CAPSULE SUMMARY

- Improved prognosis of post-transplant melanomas may be due to early diagnosis resulting from screening of organ transplant recipients in a dedicated transplant dermatology clinic.
- The benign to malignant ratio of pigmented lesions in our cohort was 16:1.

PATIENTS AND METHODS

All patients were identified from the database of the dedicated Transplant Dermatology Clinic at the Skin and Cancer Foundation (SCF). Dermatologists with a special interest in transplant medicine operate this multidisciplinary clinic with surgical support from dermatologic and plastic surgeons.

Patients are referred to the clinic by transplant physicians, general practitioners, and other dermatologists. During their appointment, a specialist dermatologist examined each patient using dermoscopy. Suspicious pigmented lesions were excised for histopathologic analysis. Lesions that were suspicious for keratinocyte cancers were also biopsied and treated. Patients were given verbal advice on their increased risk of skin cancer and educated on sun-protection measures such as sunscreen, clothing, and sun avoidance. Patients were also advised to present urgently if they had any concerns about a skin lesion, including change in size, shape, or color.

High-risk patients with multiple keratinocyte cancers are seen every 3 to 4 months, intermediate-risk patients are seen every 6 months, and low-risk patients are reviewed annually. Patients with post-transplant malignant melanoma were treated and monitored every 3 months for 2 years, then every 6 months thereafter. These intervals are similar to those in clinical guidelines that recommend review and treatment according to individual risk factors.[9-13]

Demographic, clinical, and histopathologic data are entered prospectively into the SCF database. We reviewed the database and histopathology reports for all consecutive patients under the care of the SCF dedicated Transplant Dermatology Clinic between January 1, 2006, and December 31, 2015 (120 months).

Data collected included the age at transplant, age at melanoma diagnosis, the time interval between transplant and melanoma (taken from the first transplant where there were more than one), type and dose of immunosuppressive therapy at melanoma diagnosis, and site of occurrence of melanoma. Other relevant data collected included history of other skin malignancies, including atypical nevi and previous biopsies performed, skin phototype, and history of excessive sun exposure. In addition, patients were asked about history of previous melanomas and their family history of melanoma and nonmelanoma skin cancers.

We also audited all biopsied pigmented skin lesions in OTRs to determine the ratio of benign to malignant excised pigmented lesions. We extracted age at biopsy, anatomic location of the biopsied lesion, histopathologic diagnosis of the specimen, and the type of biopsy.

All histopathologic diagnoses were made or confirmed by consultant pathologists with an interest in dermatopathology. All melanoma histology reports were subsequently reviewed by an experienced dermatopathologist (V.F). The characteristics of each melanoma were documented and included the histologic subtype, Breslow thickness, Clark level, regression, tumor-infiltrating lymphocyte, ulceration, mitoses, and contiguous nevus. Other information extracted from the database included diagnoses of cutaneous lesions, such as keratinocyte cancers, whether there was recurrence of melanoma, whether immunosuppression was changed after the melanoma diagnosis, and the total follow-up period. Short-term monitoring had not been used to diagnose any of the melanomas.

RESULTS

The study included 327 OTRs, 212 (65%) men and 115 (35%) women, including 285 renal (87%)

Abbreviations used:

mTOR: mammalian target of rapamycin
OTR: organ transplant recipient
SCF: Skin and Cancer Foundation

transplants, 18 heart (5.5%), 8 pancreatic islet cell (2.5%), 6 double- or single-lung (1.8%), 5 liver (1.5%), and 4 pancreas (1.2%). One patient had a hand transplant.

The mean age at first transplantation was 43.0 ± 14.8 years. The mean duration of immunosuppression to the end of the study period was 13.9 ± 8.7 years. The mean number of visits to the clinic was 8.2 ± 8.9 (median, 12; range, 1-43 visits). For the 275 OTRs with more than 1 visit, the mean duration of follow up was 4.7 ± 3.2 years (range, 0.1-9.8 years).

There were 11 incident primary melanomas diagnosed in 10 patients (1 patient had 2 primary melanomas); of these, 5 were in situ and 6 were invasive. The male-to-female ratio was 8:2 (Table I). Nine of the 10 patients (90%) were renal transplant recipients, and 1 was a heart recipient.

The melanoma locations were the upper limbs in 4, the head and neck in 3, trunk in 2, and lower limbs in 2. The mean interval between the first transplant and diagnosis of melanoma was 5.5 years (range, 0-19 years). The mean follow-up duration after the melanoma diagnosis was 7.5 years (range, 2.0-9.7 years).

Other clinical characteristics of the OTRs diagnosed with melanoma, such as age at melanoma diagnosis and immunosuppressive treatment at melanoma diagnosis, are recorded in Table I. Of those with a melanoma diagnosis, 50% had concurrent dysplastic nevi, and 92% had a keratinocyte cancer.

Immunosuppressive regimen

Immunosuppressive treatment varied greatly in the melanoma patients. The doses and combinations varied for each patient in accordance with the clinical practice of the treating physicians.

After the melanoma diagnosis, 7 of the 10 patients had modifications to their immunosuppression regimen with the advice of both the transplant physician and the treating dermatologist. This included a decrease in dosage, removing 1 of the drugs from a 3-drug regimen, or changing a calcineurin inhibitor to a mammalian target of rapamycin (mTOR) inhibitor. Of the 10 patients who were on a calcineurin inhibitor-based 3-drug regimen, the calcineurin inhibitor was changed to an mTOR inhibitor in 4 patients, the dose of calcineurin inhibitor was decreased in 3 patients, the dose of mTOR inhibitor was decreased in 2 patients, and the immunosuppression therapy was unchanged in 3 patients.

Only 1 patient had been prescribed azathioprine, and 4 patients were prescribed oral acitretin as part of chemoprophylaxis of keratinocyte cancers. None of the patients had received other photosensitizing medications such as thiazides or voriconazole.

The patient who had 2 primary melanomas had a negative specimen on sentinel lymph node biopsy at the first diagnosis. She had local adjuvant postoperative radiotherapy to the site of her primary desmoplastic melanoma (1.04 mm thick) after wide local excision. This was a decision of the treating melanoma unit, because wide margins had been obtained and there was no evidence of perineural invasion. The other patients did not require chemotherapy or radiotherapy as part of their treatment. For all but 1 other patient, the criteria for sentinel lymph node biopsy were not met; this patient, a heart transplant recipient with a 3.8-mm-thick melanoma, declined sentinel lymph node biopsy.

Of the 11 melanomas, 8 were superficial spreading melanomas, 2 were lentigo maligna melanomas, and 1 was a desmoplastic melanoma (Table II).

Six invasive and 5 in situ melanomas developed during the observation period, a total of 1280 person-years. This corresponds to a crude invasive melanoma incidence of 468.8 per 100,000 person-years and a crude invasive and in-situ melanoma incidence of 859.4 per 100,000 years. This is approximately 15-fold and 19-fold that of the general population (age-standardized rates of 61.6 and 43.2 per 100,000 patient-years for men and women, respectively).[14]

The Breslow thickness was <1 mm in 9 of the 11 melanomas. Of the remainder, the first was a desmoplastic melanoma and 1.04 mm thick, and the second was a superficial spreading melanoma and 3.8 mm thick. Regression was absent in 7 of the 11 patients (64%) and present in 4. Seven of the melanomas were de novo (64%). A contiguous nevus was present in 4 patients, of which 2 were dysplastic.

At the end of the study period and a mean of 7.5 years of follow-up after the melanoma diagnosis (range, 2-10 years), all melanoma patients were free of disease recurrence. All melanoma patients were monitored through clinical examination. The heart transplant recipient with the 3.8-mm-thick melanoma underwent a further 6 months of ultrasound examinations of his lymph node basins.

Benign-to-malignant ratio

During the cohort follow-up, 177 suspicious nevi were biopsied, of which the specimens for 119 were

Table I. Clinical characteristics of solid organ transplant recipients diagnosed with melanoma at a dedicated transplant dermatology clinic

Patient, sex	Organ transplanted	Subtype, Breslow thickness (mm), Clark level	Age at melanoma, y	Years post-transplant	Immunosuppressive treatment at melanoma diagnosis	Chemoprophylaxis	Site of melanoma	Other biopsy-proven skin lesions before melanoma diagnosis	Immunosuppression change at melanoma diagnosis	Follow-up period before melanoma diagnosis, mo	Follow-up period after melanoma diagnosis, mo
1 M	Renal	LMM, in situ, 1	63	19	Aza, Cyclo	Acitretin	R forehead	11 BCC, 2 Bowen disease, ≥7 SCC	Aza dose decreased, Cyclo changed to SRL	111	18
2 M	Renal	SSM, in situ, 1	61	4	MMF, Pred, Tacro	Nil	Mid lower back	1 SK, 1 SCC	Tacro changed to ERL	66	38
3 M	Renal	LMM, in situ, 1	52	1	MMF, Pred, Tacro	Nil	R cheek	1 SK, 1 Bowen disease, 2 SCC	Unchanged	6	97
4 F	Renal	SSM, in situ, 1	35	4	MMF, Pred, SRL	Nil	R neck	1 dysplastic nevus	Unchanged	23	104
5 F	Renal	MM, in situ, 1	47	4	Cyclo, MMF, Pred	Nil	R upper arm	17 dysplastic nevi, 1 SK, 1 BCC, 1 Bowen disease	Cyclo dose decreased	22	72
5 F	Renal	Desmoplastic MM, 1.04, 4	46	3	Cyclo, MMF, Pred	Nil	R upper arm	17 dysplastic nevi, 1 SK, 1 BCC, 1 Bowen disease	Cyclo dose decreased	11	84
6 M	Renal	SSM, 0.2, 2	52	10	MMF, Pred, Tacro	Acitretin	R lower leg	1 dysplastic nevus, ≥3 BCC, 1 SCC	Unchanged	11	78
7 M	Renal	SSM, 0.6, 2	68	5	MMF, Pred, SRL	Acitretin	L forehead	1 SK, ≥15 BCC, 1 Bowen disease, ≥7 SCC	SRL dose decreased	20	72

8 M	Renal	SSM, 0.8, 3	56	1	MMF, Pred, Tacro	Nil	L mid back	3 dysplastic nevi, 1 SK ≥9 BCC, 1 Bowen disease, ≥6 SCC	Tacro changed to SRL	16	77
9 M	Renal	SSM, 0.82, 3	56	7	MMF, Pred, Tacro	Nil	R posterior shoulder	≥8 BCC	Tacro changed to SRL, Pred dose decreased	17	72
10 M	Heart	SSM, 3.8, 4	65	11	MMF, Pred, SRL	Acitretin	L upper thigh	1 SK, ≥10 BCC, 1 Bowen disease, ≥10 SCC	Pred and SRL dose decreased	42	48

Aza, Azathioprine; *BCC*, basal cell carcinoma; *Bowen disease*, squamous cell carcinoma in situ; *Cyclo*, cyclosporine; *ERL*, everolimus; *F*, female; *LMM*, lentigo maligna melanoma; *M*, male; *MM*, malignant melanoma; *MMF*, mycophenolate mofetil; *Pred*, prednisolone; *SCC*, squamous cell carcinoma; *SK*, solar keratosis; *SRL*, sirolimus; *SSM*, superficial spreading melanoma; *Tacro*, tacrolimus.

benign, 47 were dysplastic, and 11 were confirmed melanomas. Therefore, the number needed to excise was 16; that is, for every melanoma diagnosed, 16 benign or dysplastic pigmented nevi were biopsied.

Discussion

During 10-year period, we diagnosed 5 in situ and 6 invasive melanomas in a cohort of OTRs referred to a dedicated transplant dermatology clinic. Of the invasive melanomas, only 2 had a Breslow thickness >1 mm. After an average 7.5 years of follow-up from the melanoma diagnosis, all patients remained recurrence free and alive.

The outcome from our patient group appears more favorable than published data for population-based cohorts of transplant recipients. Previous studies have reported that de novo melanomas that occur after transplant are associated with greater Breslow thicknesses and worse survival outcomes.[2,15,16] A population-based study of melanomas in Australian renal transplant recipients found that the mortality rate of de novo melanomas was 76% over a median of 6.6 years of follow-up.[8] In our cohort, only 2 patients had a melanoma >1 mm thick.

We believe our diagnosis of thin de novo post-transplant melanomas and subsequent good prognosis was due to increased vigilance and screening in this cohort. Patients were referred to our service as part of routine skin surveillance, not just when there was a suspicious lesion. Patients were therefore being monitored before the melanoma diagnosis. Education on skin surveillance and photo protection commences on the first visit to our service, which may improve patient self-detection of suspicious changes. On subsequent visits to the SCF Transplant Dermatology Clinic, patients reported improved sun protection compliance as well as performing regular self-skin examinations as a result of the education provided at the SCF Clinic.

A study of renal transplant recipients in Victoria, which included some patients who attended our clinic, showed that the sun-associated risk behavior of these patients was significantly better than the general population, especially with regard to the use of sunscreens and clothing.[17]

The melanomas in our cohort were more likely to originate on sun-exposed anatomic sites (64% on the head and neck, face, or upper limbs) unlike other studies that found melanomas occurred most frequently on the trunk of transplant recipients.[2,7,17] This anatomic distribution is similar to that observed for melanomas occurring in the Australian (Queensland) general population.[18]

Table II. Histopathologic characteristics of melanomas arising in solid organ transplant recipients diagnosed in a dedicated transplant dermatology clinic

Patient	Type	In situ or invasive	Thickness, mm	Clark level	Regression	Nevus or de novo	Tumour-infiltrating lymphocyte	Ulceration	Mitotic rate, per mm
1	LMM	In situ	NA	1	No	De novo	NA	Absent	NA
2	SSM	In situ	NA	1	No	Nevus (intradermal)	Absent	Absent	NA
3	LMM	In situ	NA	1	No	De novo	Absent	Absent	NA
4	SSM	In situ	NA	1	Yes	Nevus (dysplastic)	NA	Absent	NA
5	Desmoplastic MM	Invasive	1.04	4	No	Nevus (dysplastic)	Absent	Absent	0
5	MM	In situ	NA	1	No	De novo	NA	Absent	0
6	SSMM	Invasive	0.2	2	Yes	De novo	Absent	Absent	0
7	SSMM	Invasive	0.6	2	No	De novo	Absent	Absent	1
8	SSM	Invasive	0.8	3	Yes	Nevus (compound melanocytic)	Absent	Absent	0
9	SSM	Invasive	0.82	3	No	De novo	Absent	Absent	1
10	SSM	Invasive	3.8	4	Yes	De novo	Small numbers present	Absent	6

LMM, Lentigo maligna melanoma; *MM*, malignant melanoma; *NA*, not applicable; *SSM*, superficial spreading melanoma; *SSMM*, superficial spreading malignant melanoma.

Previous studies have reported melanomas in transplant recipients arising in most cases in precursor dysplastic nevi.[14,19] In contrast, melanomas from precursor lesions developed in only 4 of 11 patients (36%) in our cohort, similar to the 33% reported by Le Mire et al. (33%).[3]

In terms of risks, melanoma developed in 10 of 11 patients (90.1%) who had a prior diagnosis of keratinocyte cancer. In addition, 5 patients (45%) had also had prior histologic diagnosis of dysplastic nevi. Hence, we recommend that all OTRs be evaluated and monitored according to their individual risk factors. Patients with dysplastic nevi should be monitored at least annually,[14] particularly looking out for new nevi.

Serial dermoscopy can improve the preoperative diagnostic accuracy of cutaneous melanoma and has a role in the monitoring of some nevi.[19] In addition to improved sensitivity, serial dermoscopy is shown to reduce unnecessary excisions of benign nevi. The comparison of dermoscopic images helps detect subtle changes that may indicate cutaneous melanoma.[18] When available, reflectance confocal microscopy could also play a role in detecting melanomas in this patient cohort because it can detect malignant features in clinically and dermoscopically subtle, questionable lesions and can improve the benign-to-malignant biopsy ratio.[20] However, these microscopes are not widely available, so there may be access issues for some patients. Patients should be educated on the signs of melanoma, especially new nevi, and taught how to perform self-checks with the help of family members.

For every 1 melanoma diagnosed in our cohort of transplant patients, 16 pigmented nevi were biopsied. To our knowledge, there are no prior data on the number needed to excise for pigmented lesions in a transplant cohort. The number needed to excise of pigmented lesions in the immunocompetent dermatology population is approximately 5:1. In our clinical experience, some of the melanomas appearing in transplant recipients are clinical and dermoscopically bland. Given that this is a high-risk group, we opted for excision of any concerning pigmented lesion ahead of short-term follow-up with serial photography. This explains our elevated benign-to-malignant ratio. However, this approach may be justified due to the poorer prognosis of de novo transplant melanomas in Australia.[3,7,8,11]

Where a primary invasive melanoma has been detected in an OTR, reduction of immunosuppression or switching from a calcineurin inhibitor to an mTOR inhibitor, or both, is thought to be a reasonable and effective adjuvant treatment strategy to surgical excision, according to expert consensus.[21]

The immunosuppression was reduced or the calcineurin inhibitor was replaced with mTOR inhibitors in all but 1 of our patients with invasive melanoma. In the case of multidrug regimens, the agent discontinued was tacrolimus in 3 of 10 patients.

There is currently a scarcity of reliable data to guide the clinical management of melanomas in transplant recipients.

A strength of this study is that all skin cancers were histopathologically proven. In addition, the patients' full medical records were available; therefore, we had complete capture of clinical and histopathologic information.

Study limitations include crude incidence rates, which are not age standardized, unlike the comparison rates of melanoma in the general population. The cohort is small but representative of a high-risk subset.

CONCLUSION

Our data indicate that increased surveillance and expert dermatologic management of OTR in a dedicated transplant dermatology clinic may result in earlier diagnosis of melanomas and reduce the proportion of OTRs presenting with thick melanomas. It may also improve patient outcomes, although we acknowledge our cohort is small, and a good survival profile is anticipated for the 5 patients with in situ melanomas.

Owing to the increased risk of multiple types of skin cancers in transplant recipients, suspicious pigmented lesions should be excised promptly and unnecessary ultraviolet radiation exposure minimized. Close monitoring after transplantation is warranted, particularly for patients with risk factors for melanoma. In addition, primary prevention through adopting sun-protective behavior and regular medical surveillance for all patients undergoing organ transplantation is paramount.

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