Nephro-Urol Mon. 2017 September; 9(5):e59535. doi: 10.5812/numonthly.59535.

Published online 2017 July 4. **Brief Report**

Melanoma Risk in Renal Transplanted Patients

Giovanni Cavaliere,[1] Elisa Zavattaro,[2] Federica Veronese,[3] Paolo Fava,[4] and Paola Savoia[3,*]

[1]Department of Medical Science, University of Turin, Torino, Italy
[2]Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy
[3]Department of Health Science, University of Eastern Piedmont, Novara, Italy
[4]AOU Citta Della Salute e Della Scienza, Torino, Italy

[*]*Corresponding author*: Paola Savoia, Department of Health Science, University of Eastern Piedmont, Via Solaroli 17, 28100 Novara, Italy. Tel: +39-3213733387, Fax: +39-3213733387, E-mail: paola.savoia@med.uniupo.it

Received 2017 April 06; **Revised** 2017 April 21; **Accepted** 2017 June 10.

Abstract

Despite the well-known increased risk to develop non-melanoma skin cancer (NMSC) due to the long-term immunosuppression, data about melanoma incidence and prognosis in solid organ transplanted patients are still debated. Literature studies report a relative risk for melanoma varying from 1.2 and 5.8 in different solid organ recipients, probably as a consequence of the difference in immunosuppressive treatments and endogenous and exogenous risk factors. Here we report data about melanoma incidence, prognosis and clinicopathological characteristics in a series of 686 kidney transplant recipients. In this series, melanoma incidence was 3.5%; most cases were represented by in situ or thin melanomas mainly related to sun exposure, and the prognosis of our patients was good except for only one case with a progressive disease. Our experience confirms the importance of a regular dermatological follow-up and of education to correct sun exposure even in transplanted patients.

Keywords: Melanoma, Skin Tumours, Solid Organ Transplantation, Immunosuppression

1. Background

The crucial role of long-term immunosuppressive treatment as a promoter for malignancy has been extensively established in literature (1), and the increased risk for non-melanoma skin cancer (NMSC) in solid organ transplant recipients is well known (2, 3).

Conversely, data about melanoma incidence and behaviour in transplanted patients are still debated, despite the fact that the impact of the immune system on the onset and progression of this cancer has been clearly demonstrated (4, 5).

A large analysis performed on an Australian cohort of kidney transplant recipients reported a melanoma incidence of almost 1% closely related to iatrogenic immunosuppression and confined to the period of transplant function (1). Therefore, a systematic review was recently performed on a 20 cohort study (6), identifying an aggregate relative risk (RR) for melanoma of 2.71 among transplanted patients; this risk was higher (5.27) for liver and heart recipients and lower (2.54) for kidney recipients, probably due to the differences in immunosuppressive regimens. However, several differences have been demonstrated in various studies and the RR ranged from 0.8 (7) to 5.80 (8), probably due to the heterogeneity of the inclusion criteria and the follow-up length and to the variability of the ethnic and geographic origin of patients. The well-known risk factors for melanoma such as fair skin, presence of atypical nevi, family history for melanoma, and personal history of sunburns could also play a crucial role creating a favourable substrate on which immunosuppression acts as a triggering factor.

Here we revised our series of kidney transplant recipients undergoing a regular dermatological follow-up with the aim of evaluating the melanoma incidence within this group of patients, its characteristics, and the possible relationship between the onset of this tumour and eventual exogenous and endogenous risk factors.

Clinical outcome was also evaluated to establish the possible immunosuppression impact on the disease progression.

2. Methods

2.1. Patients

A total of 686 kidney transplant recipients who underwent a regular dermatological follow-up were included in this study. Dermatological consultations were performed between April 1997 and December 2016. Our sample consisted in 401 males and 285 females with a median age of

50 years at transplantation and of 60 at the last follow-up visit and a median duration of immunosuppression of 8.9 years. Clinical information about the patients' endogenous and exogenous risk factors for skin tumours were recorded and a complete dermatological examination was performed at each scheduled visit. We collected, also, information about immunosuppressive schedules which the patients had undergone.

3. Results

3.1. Clinical Characteristics

The number of the patients who developed a cutaneous melanoma in the post-transplantation period was 24 accounting for 3.5% of our series. Seventeen patients were males and 7 females, with a median age at melanoma diagnosis of 57 years (ranging from 36 to 78). For these patients, the median age at transplantation was 49 years (ranging from 25 to 64), and the median time of immunosuppression was 13 years (ranging from 3 to 22); the median duration of the dermatological follow-up was 8.9 years. The median time of melanoma onset from transplantation was 5.3 years (ranging from 0.7 to 14.6). Interestingly, 2 out of 24 patients developed multiple melanomas. One out of these developed a second melanoma 13 months after the first diagnosis, whereas the other one developed 3 melanomas after 19 and 53 months from the first diagnosis, respectively. Clinical data of these patients are reported in Table 1.

Moreover, 4 patients affected by melanoma developed also a NMSC. All these lesions were diagnosed as basal cell carcinoma (BCC); in two cases, the onset of BCC preceded melanoma diagnosis, while in the other two it occurred subsequently.

3.2. Histology

Eleven out of 24 of total excised melanomas were histologically in situ melanomas; the median Breslow's thickness of other lesions was 1.12 mm (ranging from 0.5 to 4 mm). Data about histological characteristics are summarized in Table 2.

3.3. Risk Factors

The skin phototype predominantly represented in our series (66.6%) was III according to the characteristics of the patients pertaining to our geographical area. Two patients reported a history of sunburns at a young age and the other 6 reported frequent sun exposure without photoprotection. Two patients had working outdoor activities, whereas nobody reported family history of melanoma. We found no significant correlation between the type of immunosuppressive schedule and melanoma onset.

From the transplanted patients affected by melanoma, of our series, only one developed metastatic melanoma with lung and distant nodal metastases.

4. Discussion

It has been demonstrated that the immune surveillance plays a fundamental role in the pathogenesis of melanoma (4), as confirmed by the importance of immunotherapeutic approach in the treatment of advanced stages of this disease (9). However, while data concerning the higher risk of NMSC after transplantation are well established (2, 3, 10), not all authors agree about the increase in melanoma risk in transplant recipients (1, 6-12).

In a previous review of our series (13), the 3.9% of kidney recipients who underwent a regular dermatological follow-up suffered from melanoma; the percentage of patients affected by NMSC in the same series was 24.8%. Here, a series significantly increased in number and a longer follow-up enabled us to identify a percentage of patients affected by melanoma accounting for 3.5%. In literature, the pick of melanoma onset in immunosuppressed patients is reported during the second year from transplantation (1); on the contrary, in our experience the median time of melanoma onset was 5.3 years, suggesting a potential role of cumulative low-dose immunosuppression. Moreover, even if cyclosporine and/or azatyoprine-based immunosuppressive regimens showed a significant correlation with the risk of developing skin cancer in most published studies (14-17), we did not find any significant correlation with the treatment schedule.

We think that endogenous and exogenous risk factors can play a major role in the pathogenesis of melanoma and, also, in transplanted patients. Differences in skin phototype and in UV radiation exposure, as well as in the ethnic and geographical origin of transplanted patients could explain differences in melanoma prevalence among the transplanted population in different countries (1, 6-8, 12, 18), justifying the fact that in our series, the incidence of melanoma is higher than what is described in other large studies recently published (7). In our series, most patients showed a phototype III, in accordance with their origin from the Mediterranean area; however, almost half of them reported previous significant sun exposure for recreational reasons or outdoor work, suggesting that immunosuppression could be a simple trigger on a pre-existing condition of susceptibility. This hypothesis is supported by the onset of multiple melanomas in two of our patients and by the fact that in both, there was a concordance between sites in which the lesions arise. The site concordance

Table 1. Clinical Characteristics of Transplanted Patients Affected by Multiple Melanomas

Gender	Site	Istological Type	Breslow	Time from Transplantation	Time from First Diagnosis	
M	Foot	ALM	4	16.9 y		1st melanoma
	Foot	ALM	0.8	18 y	13 mo	2nd melanoma
F	Trunk	SSM	In situ	5.9 y		1st melanoma
	Trunk	SSM	In situ	7.4 y	18 mo	2nd melanoma
	Trunk	LMM	0.6	10.2 y	52 mo	3th melanoma

Table 2. Clinical and Histological Characteristics of Melanomas Diagnosed in Transplanted Patients

Variable	Value
Gender	
M	17
F	7
Age	57 y (range 36 - 78)
Site	
Trunk	11
Upper limbs	1
Lower limbs	7
Foot	4
Head	3
Other	1
Histological type	
SSM	19
NM	1
ALM	4
LMM	2
Mucosal	1
Breslow thickness	1.12 mm (range 0.5 - 4 mm)

Abbreviations: ALM, acral-lentiginous melanoma; LMM, lentigo maligna melanom; NM, nodular melanoma; SSM, superficial spreading melanoma.

for patients affected by multiple melanomas justify, in fact, the assumption that the risk is mainly related to the previous UV damage (11, 19). The role of the photo exposition is also confirmed by the diagnosis of BCC in other four patients.

In our experience, more than 45% of our patients (11/24) had an in-situ melanoma; for other patients, the median Breslow thickness was relatively low with a high prevalence of Superficial Spreading Melanoma. These observations support, on the one hand, the relatively low aggressiveness of melanomas diagnosed in kidney transplanted patient; on the other hand, the major role of dermatological follow-up. In most patients, in fact, the diagnosis was made incidentally during a routinely programmed visit.

Literature data regarding the clinical course of melanoma developed in the post-transplant period are scanty. However, the thickness of the primary lesion and the known prognostic factors seems to regulate the course of the disease even in transplanted patients (20) and the outcome of patients with thicker melanoma is worse than that of patients with thinner lesions. No deaths are in fact reported for transplant recipients with in situ or thin melanomas (21). Also, in our experience, the only one patient who developed a progressive disease was affected by a 4-mm ALM that metastasised to distant lymph node and lung.

Future studies are needed to better characterize the melanoma risk and the outcome in transplant recipients. However, also in this group of patients, early diagnosis is critical and dedicated dermatologic follow-up programs are fundamental; in view of the role of sun exposure, we also underline the importance of the constant education to the photoprotection in transplanted patients.

References

1. Vajdic CM, van Leeuwen MT, Webster AC, McCredie MR, Stewart JH, Chapman JR, et al. Cutaneous melanoma is related to immune suppression in kidney transplant recipients. *Cancer Epidemiol Biomarkers Prev.* 2009;**18**(8):2297–303. doi: 10.1158/1055-9965.EPI-09-0278. [PubMed: 19622722].
2. Gallagher MP, Kelly PJ, Jardine M, Perkovic V, Cass A, Craig JC, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol.* 2010;**21**(5):852–8. doi: 10.1681/ASN.2009101043. [PubMed: 20431040].
3. Ingvar A, Smedby KE, Lindelof B, Fernberg P, Bellocco R, Tufveson G, et al. Immunosuppressive treatment after solid organ transplantation and risk of post-transplant cutaneous squamous cell carcinoma. *Nephrol Dial Transplant.* 2010;**25**(8):2764–71. doi: 10.1093/ndt/gfp425. [PubMed: 19729465].
4. Dean JH, Greene MH, Reimer RR, LeSane FV, McKeen EA, Mulvihill JJ, et al. Immunologic abnormalities in melanoma-prone families. *J Natl Cancer Inst.* 1979;**63**(5):1139–45. [PubMed: 159376].
5. Belloni-Fortina A, Piaserico S, Tonin E, Alaibac M. Melanoma and immunosuppression. *Dermatology.* 2009;**218**(1):88. doi: 10.1159/000161125. [PubMed: 18832814] author reply 89.

6. Green AC, Olsen CM. Increased risk of melanoma in organ transplant recipients: systematic review and meta-analysis of cohort studies. *Acta Derm Venereol.* 2015;**95**(8):923–7. doi: 10.2340/00015555-2148. [PubMed: 26012553].
7. Einollahi B, Nemati E, Lessan-Pezeshki M, Simforoosh N, Nourbala MH, Rostami Z, et al. Skin cancer after renal transplantation: Results of a multicenter study in Iran. *Ann Transplant.* 2010;**15**(3):44–50. [PubMed: 20877266].
8. Chatrath H, Berman K, Vuppalanchi R, Slaven J, Kwo P, Tector AJ, et al. De novo malignancy post-liver transplantation: a single center, population controlled study. *Clin Transplant.* 2013;**27**(4):582–90. doi: 10.1111/ctr.12171. [PubMed: 23808800].
9. Lee CS, Thomas CM, Ng KE. An Overview of the Changing Landscape of Treatment for Advanced Melanoma. *Pharmacotherapy.* 2017;**37**(3):319–33. doi: 10.1002/phar.1895. [PubMed: 28052356].
10. Jensen AO, Svaerke C, Farkas D, Pedersen L, Kragballe K, Sorensen HT. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. *Acta Derm Venereol.* 2010;**90**(5):474–9. doi: 10.2340/00015555-0919. [PubMed: 20814621].
11. Lindelof B, Sigurgeirsson B, Gabel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol.* 2000;**143**(3):513–9. [PubMed: 10971322].
12. Einollahi B, Rostami Z, Nourbala MH, Lessan-Pezeshki M, Simforoosh N, Nemati E, et al. Incidence of malignancy after living kidney transplantation: a multicenter study from iran. *J Cancer.* 2012;**3**:246–56. doi: 10.7150/jca.3042. [PubMed: 22712025].
13. Savoia P, Stroppiana E, Cavaliere G, Osella-Abate S, Mezza E, Segoloni GP, et al. Skin cancers and other cutaneous diseases in renal transplant recipients: a single Italian center observational study. *Eur J Dermatol.* 2011;**21**(2):242–7. doi: 10.1684/ejd.2011.1272. [PubMed: 21382788].
14. Fekecs T, Kadar Z, Battyani Z, Kalmar-Nagy K, Szakaly P, Horvath OP, et al. Incidence of nonmelanoma skin cancer after human organ transplantation: single-center experience in Hungary. *Transplant Proc.* 2010;**42**(6):2333–5. doi: 10.1016/j.transproceed.2010.05.021. [PubMed: 20692474].
15. Keller B, Braathen LR, Marti HP, Hunger RE. Skin cancers in renal transplant recipients: a description of the renal transplant cohort in Bern. *Swiss Med Wkly.* 2010;**140**:w13036. doi: 10.4414/smw.2010.13036. [PubMed: 20652847].
16. Mackenzie KA, Wells JE, Lynn KL, Simcock JW, Robinson BA, Roake JA, et al. First and subsequent nonmelanoma skin cancers: incidence and predictors in a population of New Zealand renal transplant recipients. *Nephrol Dial Transplant.* 2010;**25**(1):300–6. doi: 10.1093/ndt/gfp482. [PubMed: 19783601].
17. Bernat Garcia J, Morales Suarez-Varela M, Vilata JJ, Marquina A, Pallardo L, Crespo J. Risk factors for non-melanoma skin cancer in kidney transplant patients in a Spanish population in the Mediterranean region. *Acta Derm Venereol.* 2013;**93**(4):422–7. doi: 10.2340/00015555-1525. [PubMed: 23303600].
18. Dinh QQ, Chong AH. Melanoma in organ transplant recipients: the old enemy finds a new battleground. *Australas J Dermatol.* 2007;**48**(4):199–207. doi: 10.1111/j.1440-0960.2007.00387.x. [PubMed: 17956476].
19. Kricker A, Armstrong BK, Goumas C, Litchfield M, Begg CB, Hummer AJ, et al. Ambient UV, personal sun exposure and risk of multiple primary melanomas. *Cancer Causes Control.* 2007;**18**(3):295–304. doi: 10.1007/s10552-006-0091-x. [PubMed: 17206532].
20. Leveque L, Dalac S, Dompmartin A, Louvet S, Euvrard S, Catteau B, et al. [Melanoma in organ transplant patients]. *Ann Dermatol Venereol.* 2000;**127**(2):160–5. [PubMed: 10739973].
21. Zwald FO, Christenson LJ, Billingsley EM, Zeitouni NC, Ratner D, Bordeaux J, et al. Melanoma in solid organ transplant recipients. *Am J Transplant.* 2010;**10**(5):1297–304. doi: 10.1111/j.1600-6143.2010.03078.x. [PubMed: 20353465].