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INVESTIGATIVE REPORT

Risk Factors for Non-melanoma Skin Cancer in Kidney Transplant Patients in a Spanish Population in the Mediterranean Region

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Non-melanoma skin cancer (NMSC) is the most frequent malignancy in organ transplant recipients. The aetiology of NMSC after transplant is multifactorial. The aim of this study was to determine the clinical and environmental factors involved in the development of NMSC in a Spanish kidney transplant population from the Mediterranean region. A total of 289 patients who had received a kidney transplant during the period January 1996 to December 2010 were included in the study. Both prospective and retrospective data were used. All patients underwent a structured interview and a complete examination of the skin. After a median follow-up of 72 months (range 12–180 months), 73 of the 289 patients (25.2%) developed 162 tumours. The ratio of basal cell carcinoma to squamous cell carcinoma was 2.21:1. The cumulative incidence of NMSC increased with the duration of immunosuppression, from 20.78% at 5 years, to 37.35% at 10 years to 53.08% at 15 years after transplantation. Age at the time of transplant, phototype and occupational sun exposure were associated with a higher risk of NMSC. NMSC is a significant clinical problem in kidney transplant recipients. This has implications for the development of prevention and surveillance strategies. Clinical and environmental factors may be used to identify those patients who are at risk for NMSC. *Key words: transplant; renal; skin cancer; immunosuppression; risk factors; sun exposure.*

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Non-melanoma skin cancer (NMSC) is the most common cancer in kidney transplant patients (1, 2). In general, transplant patients develop these tumours at earlier ages than the general population. Some patients develop multiple tumours that behave more aggressively with considerable morbidity and potential mortality (3). In addition, transplant patients are becoming more common in dermatology consultations due to the increased frequency of transplants and the increased survival of recipients. According to the National Transplant Organization in Spain, annual kidney transplants have increased from 873 in 1988 to 2,498 in 2011 (53 kidney transplants per million population). Early diagnosis of premalignant lesions and NMSC is fundamental for reducing skin complications in these patients.

We performed an observational study with the kidney transplant population from the Mediterranean region between January 1996 and December 2010. A combination of retrospective and prospective data was examined in order to determine the association between phenotypic, clinical and environmental factors with the onset of NMSC. The Cox proportional risk model was used to identify the risk factors associated with the development of NMSC. These factors may constitute the foundation for developing clinically useful predictive indices.

MATERIALS AND METHODS

Patients

Data were collected from 289 patients who had received a kidney transplant at the Doctor Peset University Hospital in Valencia, Spain, from January 1996 to December 2010. During this period 622 kidney transplants were performed in this hospital. The patients were voluntarily recruited between January 2010 and January 2012 (end date of the study), and underwent a structured questionnaire completed by a dermatologist and a complete skin examination with subsequent follow-up visits every 6 months until the study was finalized. The study was approved by the hospital's ethics committee. All patients provided written consent.

Demographic, clinical and environmental exposure data

Demographic information on age, race, gender, follow-up time, eye colour and Fitzpatrick phototype (I–IV) was collected. Pre-transplant occupational sun exposure was used as the marker of ultraviolet (UV) radiation exposure (considered to be high when the patient had worked more than 3 years in the open air).

Other environmental factors studied were tobacco and alcohol consumption and a family history of cancer.

We also collected the duration and type of dialysis, cause of kidney failure and number of human leukocyte antigen (HLA) matches between the recipient and donor.

We grouped patients into 4 groups according to the maintenance immunosuppressor treatment: group A (mTOR-sirolimus and/or everolimus inhibitors+mycophenolate), group B (tacroli-

mus + mycophenolate), group C (cyclosporine + mycophenolate) and group D (older regimens with azathioprine).

Induction treatment was also evaluated by dividing the patients into 5 groups: group 0 (did not receive induction therapy), group 1 (induction with basiliximab: Simulect®, Novartis Farm, Barcelona, Spain), group 2 (induction with rabbit anti-thymocyte globulin: Thymoglobulin® Genzyme Europe Bv, Naarden, The Netherlands), group 3 (induction with equine anti-thymocyte globulin: ATGAM® Pfizer, Madrid, Spain) and group 4 (induction with monomurab-CD3: OKT3® Janssen, Madrid, Spain).

Skin cancer data

The number of basal cell carcinomas (BCC), squamous cell carcinomas (SCC), Bowen's disease (SCC *in situ*) and keratoacanthomas were recorded. The presence of actinic keratosis and viral warts was also noted. Diagnosis of warts and actinic keratosis was based on clinical criteria, but only histologically-confirmed cases of NMSC were included in the study. Patients were fully undressed for follow-up visits. Lesions that were suspicious of malignancy were biopsied for histological diagnosis.

Statistical analyses

Statistical analysis was carried out using SPSS version 19. The risk of skin cancer was examined using the presence of NMSC as the end-point. The continuous variables were expressed as minimum, median and maximum values. The nominal variables were expressed in absolute values and percentages. The cumulative incidence of skin cancer was calculated using the Kaplan–Meier method.

The statistical association between the risk of developing skin cancer and the risk factors studied were evaluated by univariate analysis. In order to finally identify the individual risk of each of these factors, a multivariate analysis was performed using the Cox proportional risks model.

RESULTS

General patient characteristics

We studied 305 patients who underwent kidney transplantation at the Doctor Peset University Hospital in Valencia, Spain, from January 1996 to December 2010. We excluded 16 patients (15 patients due to have received more than one transplant and one patient due to death during follow-up), with a total of 289 patients included in the study. The median follow-up was 72 months (range 12–180 months).

Mean age at the time of transplant was 52.2 years (range 13–78 years).

The clinical and demographic characteristics of the patients are shown in Table I.

Table I. *Clinical characteristics of 289 patients with kidney transplant*

	Skin cancer	
	Without (n = 216) n (%)	With (n = 73) n (%)
Age at first transplantation, years	51 (13–73)	56 (34–78)
Follow-up, years	5 (1–15)	10 (1–15)
Dialysis, years	3 (1–13)	3 (1–10)
Sex		
Female	90 (41.7)	29 (39.7)
Male	126 (58.3)	44 (60.3)
Phototype		
I–II	106 (49.1)	55 (75.3)
≥III	110 (50.9)	18 (24.7)
Eye colour		
Light eyes	51 (23.6)	28 (38.4)
Dark eyes	165 (76.4)	45 (61.6)
Occupational sun exposure		
Low	209 (96.8)	29 (39.7)
High	7 (3.2)	44 (60.3)
Dialysis type		
Haemodialysis	154 (71.3)	58 (79.5)
Peritoneal	46 (21.3)	6 (8.2)
Both	16 (7.4)	9 (12.3)
Human leukocyte antigen matches		
Not indicated	17 (7.9)	6 (8.2)
1–2	40 (18.5)	16 (21.9)
3–4	99 (45.8)	29 (39.7)
≥5	60 (27.8)	22 (30.1)
Immunosuppression treatment		
A	16 (7.4)	2 (2.7)
B	156 (72.2)	36 (49.3)
C	43 (19.9)	31 (42.5)
D	1 (0.5)	4 (5.5)
Induction treatment		
0	79 (36.6)	31 (42.5)
1	65 (30.1)	16 (21.9)
2	66 (30.5)	24 (32.8)
3	4 (1.9)	2 (2.7)
4	2 (0.9)	0 (0)
Non-melanoma skin cancer before transplant		
No	211 (97.7)	68 (93.2)
Yes	5 (2.3)	5 (6.9)
Warts before transplant		
No	189 (87.5)	69 (94.5)
Yes	27 (12.5)	4 (5.5)
Actinic keratosis before transplant		
No	115 (53.2)	46 (63.0)
Yes	101 (46.8)	27 (37.0)
Warts after transplant		
No	115 (53.2)	46 (63.0)
Yes	101 (46.8)	27 (37.0)
Actinic keratosis after transplant		
No	170 (78.7)	13 (17.8)
Yes	46 (21.3)	60 (82.2)

Skin cancer

Of the 289 patients, 73 (25.2%) developed a total of 162 NMSC, of which 41 were SCC, 91 BCC, 25 Bowen's disease and 5 keratoacanthomas. The BCC/SCC ratio was 2.21:1. If we consider only the NMSC appearing in the first 5 years, the respective ratio was 3.5, indicating an earlier relative BCC appearance. Of the 73 patients who developed NMSC, 38 had only 1 tumour, 30 had between 2 and 5 tumours and 5 patients developed more than 5 tumours. Of the 289 patients, 10 had developed some type of NMSC prior to transplant. Five of these 10 patients continued developing NMSC after the transplant.

The mean time from transplant until diagnosis of the first NMSC was 58.5 months.

The tumours appeared predominantly in areas exposed to the sun (head, neck and distal region of the extremities), but 20% of tumours appeared in relatively non-exposed areas. Most tumours in these latter areas were BCC.

The cumulative incidence for the development of skin cancer showed an ascending curve, going from 20.78% 5 years after transplant, to 37.35% 10 years after transplant, and 53.08% 15 years after transplant (Fig. 1).

Age at time of transplant

Age at time of transplantation was significantly associated with an increase in the risk of NMSC on univariate and multivariate analysis.

UV exposure

White skin (phototypes I/II) and light-coloured eyes were significantly associated with a higher risk of NMSC. High pre-transplant occupational sun exposure was associated with a 4-fold increased risk of NMSC vs. patients with low exposure on the univariate analysis.

On the multivariate analysis, only low phototype and high pre-transplant occupational sun exposure achieved statistical significance.

Human leukocyte antigen

Patients with a higher number of HLA matches had a lower risk of the onset of NMSC on univariate analysis, but this trend was not seen on multivariate analysis.

Immunosuppression

No statistically significant differences between the different treatments were observed. However, immunosuppression regimens with mTOR inhibitors showed a clear tendency towards a lower risk of tumours than the other treatments.

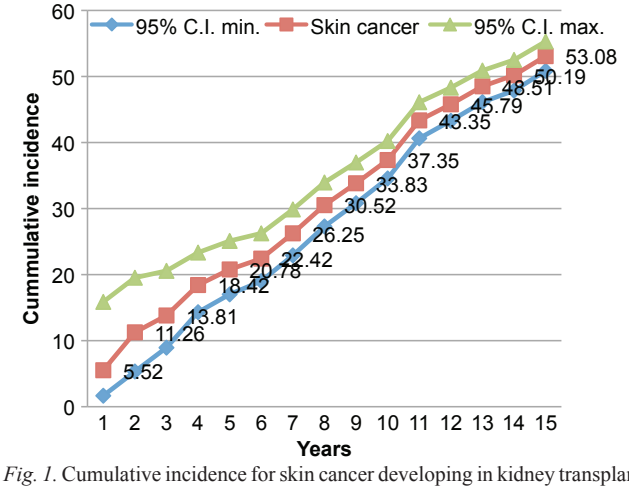

Fig. 1. Cumulative incidence for skin cancer developing in kidney transplant recipients derived from Kaplan–Meier estimation. CI: confidence interval.

No statistically significant differences were found in the risk of NMSC between patients with and without induction treatment.

Non-melanoma skin cancer prior to transplant

The presence of NMSC prior to transplant was significantly associated with an increase in the risk of NMSC on the univariate analysis, but this did not achieve statistical significance on the multivariate analysis.

Premalignant lesions and warts

After transplantation, 128 patients developed viral warts, 5 on the genital area, 40 on the palms and soles, and the rest on the trunk and extremities. Most patients developed fewer than 10 warts, only 5 patients had more than 10 warts (and all of these 5 patients developed NMSC).

The presence of actinic keratosis prior to, and after transplantation, and the detection of warts after transplantation, was associated with a higher risk of NMSC in the univariate analysis. However, this did not achieve statistical significance in the multivariate analysis.

Other clinical factors

No statistically significant associations were found between the risk of NMSC and gender, alcohol or tobacco consumption, family history of cancer, cause of renal failure and duration and type of dialysis.

Factors that were definitively associated with a higher risk of NMSC on the multivariate analysis were: age at time of transplant, low phototype and high pre-transplantation occupational sun exposure (Table II).

DISCUSSION

As in the general population, the factors that influence the risk of skin cancer after transplant are multiple and they interact (1–5). In this study, we examined a combination of phenotypic, clinical and environmental risk factors for NMSC in kidney transplant recipients using the Cox proportional risks model in order to identify the independent risk factors associated with NMSC. In addition to sun exposure, other clinical and environmental factors are associated with the risk of NMSC in this population. Accumulated UV radiation (especially UVB) is the primary carcinogenic agent responsible for NMSC induction, as suggested by the fact that the lesions appear almost exclusively in areas of skin that are exposed to UV radiation and are more numerous in patients who live in sunny countries (4, 5). Our study demonstrates that white skin and light-coloured eyes, as well as high level of occupational sun exposure, have a higher risk of NMSC after transplant.

One worrying aspect of our study is the high NMSC incidence in transplant patients compared with the rates

Table II. *Univariate analysis and final Cox proportional hazard models for risk of developing skin cancer*

	Univariate relative hazard	95% CI	*p*-value	Final Cox proportional relative hazard	95% CI	*p*-value
Age at first transplantation, years	1.09	1.06–1.12	**<0.001**	1.06	1.03–1.09	**0.001**
Dialysis, years	1.01	0.93–1.10	0.742	1.02	0.93–1.10	0.742
Sex						
Male	Ref.					
Female	0.96	0.60–1.54	0.879	0.98	0.60–1.54	0.879
Phototype						
I–II	Ref.					
≥ III	0.55	0.32–0.94	**0.029**	0.50	0.27–0.92	**0.026**
Eye colour						
Light eyes	Ref.					
Dark eyes	0.57	0.36–0.91	**0.021**	0.50	0.36–0.91	0.07
Occupational sun exposure						
Low	Ref.					
High	4.36	2.71–7.01	**<0.001**	2.15	1.25–3.71	**0.006**
Smoking habit						
No	Ref.					
Ex-smoking	1.18	0.58–2.40	0.638	1.10	0.58–2.40	0.638
Yes	1.07	0.52–2.14	0.839	1.01	0.52–2.14	0.839
Alcohol consumption						
No	Ref.					
Ex-alcohol	1.19	0.37–3.80	0.764	1.10	0.37–3.80	0.764
Yes	–	–	0.973	–	–	0.973
Family history of cancer						
No	Ref.					
Yes	1.07	0.67–1.70	0.766	1.07	0.67–1.70	0.766
Dialysis type						
Haemodialysis	Ref.					
Peritoneal	0.76	0.32–1.78	0.528	0.65	0.32–1.78	0.528
Both	1.43	0.70–2.89	0.319	1.40	0.70–2.89	0.319
Human leukocyte antigen matches						
≥5	Ref.					
3–4	1.55	0.86–2.79	0.137	1.45	0.86–2.79	0.250
1–2	2.28	1.16–4.45	**0.016**	2.15	1.16–4.45	0.060
Immunosuppression treatment						
A	Ref.					
B	1.85	0.44–7.75	0.394	1.90	0.44–7.75	0.468
C	1.41	0.34–5.98	0.636	1.35	0.34–5.98	0.635
D	1.76	0.32–9.72	0.516	1.70	0.32–9.72	0.512
Induction treatment						
0	Ref.					
1	0.81	0.44–1.47	0.489	0.75	0.44–1.47	0.320
2	0.89	0.52–1.52	0.667	0.80	0.52–1.52	0.640
3	0.59	0.14–2.48	0.473	0.45	0.14–2.48	0.455
4	–	–	0.970		–	0.890
Non-melanoma skin cancer before transplant						
No	Ref.					
Yes	3.74	1.49–9.39	**0.005**	2.35	1.49–9.39	0.070
Warts before transplant						
No	Ref.					
Yes	1.20	0.80–1.99	0.468	1.08	0.70–1.80	0.785
Actinic keratosis before transplant						
No	Ref.					
Yes	3.76	1.49–9.46	**0.005**	3.12	1.49–9.46	0.110
Warts after transplant						
No	Ref.					
Yes	1.40	1.11–1.78	**0.006**	1.18	1.00–1.50	0.190
Actinic keratosis after transplant						
No	Ref.					
Yes	4.38	2.39–8.03	**0.001**	4.15	2.39–8.03	0.320

Significant data are shown in bold.
CI: confidence interval.

reported in other European studies (2). These differences can perhaps be explained because many of the previous studies were retrospective and were based on tumour registries. The higher sun exposure in our area and the combination of retrospective and prospective data in our study may explain these differences. This incidence in our study is, however, lower than in countries such as Australia, where the highest level of NMSC after transplant has been reported, with a cumulative incidence of 52.2% at 10 years and 82.1% at 20 years (6, 7).

Age is also an important risk factor. In the study by Otley et al. (8), the risk ratio was reported to be 12 times greater in patients who received a transplant after 55 years of age compared with patients who received it before 34 years of age.

In our study the BCC/SCC ratio was 2.21:1, which contrasts with other studies where SCC is relatively more common. Again, we suggest this difference may be due to the fact that majority of previous studies are based on tumour registry data (5, 9) where, in many cases, only the primary tumour is recorded. In addition, although histopathology diagnosis is the gold standard for the diagnosis of NMSC, lesions treated without a histopathology diagnosis are not included in these registries and the incidence of BCC is not always faithfully estimated.

The importance of HLA antigen compatibility on the survival of the kidney graft is well established. Based on studies (10–12), these antigens would also play an important role on the development of tumours. In the study by Bouwes-Bavinck et al. (10), the risk of SCC was increased in recipients with HLA-B antigens mismatches. Other studies have suggested a role of specific haplotypes in tumour development. These studies showed a negative association between HLA-A11 and skin cancer in renal transplant recipients (11), and a positive association with HLA-B27 and HLA-DR7 (12). However, other studies have not confirmed these associations (13, 14). In our study, patients with a higher number of HLA matches had a lower risk of NMSC on the univariate analysis, but this association was not confirmed in the multivariate analysis.

The role of papillomavirus in the aetiopathogenesis of NMSC in transplant patients is still controversial. In the study by Bouwes-Bavinck et al. (15), actinic keratoses and warts were associated with an increased risk of NMSC compared with patients without these lesions. In our study, warts patients with actinic keratoses after transplantation showed an increased risk of NMSC in the univariate analysis, but this did not reach statistical significance in the multivariate analysis. In this regard we must bear in mind the limitations of our study. The use of retrospective data poses a greater risk of information bias, so we must consider the possibility that viral warts could have been considered a "non-serious" disorder and not included in the medical record. In a study by Arron et al. (16), the HPV genome was more frequently detected in early lesions, such as actinic keratoses and carcinomas *in situ*, rather than in the more advanced SCC, suggesting that the primary role of HPV may be in the early stages of skin carcinogenesis. Subclinical HPV infection may be significant. Studies using polymerase chain reaction (PCR) suggest that HPV may be identified in more than 80% of BCCs and SCCs in transplant populations, compared with only 30% in immunocompetent patients (17). However, the finding of HPV occurring commonly in normal skin, and the lack of particular "high-risk" HPV types, leaves the role of HPV in the development of skin cancer open.

With regards to immunosuppressor treatment, group A (mTOR inhibitors+mycophenolate) showed a lower risk of onset of NMSC than other treatments, though these results did not achieve statistical significance, probably due to the relatively low number of patients in this group. These results are concordant with other studies that suggest that mTOR inhibitors could have a preventative action in carcinogenesis (18–22). While we have been able to identify a clear tendency towards a lower incidence of NMSC with mTOR inhibitors, more cohort studies with sufficient statistical power will be needed in order to validate this tendency.

While induction treatment does appear to be clearly associated with a higher risk of the onset of lymphoproliferative disorders (23, 24), the role of this treatment in the aetiopathogenesis of skin cancer in transplant patients is not so clear and there is controversy on the subject. In our study, induction treatment did not play a role in the onset of NMSC.

Evaluation of clinical and environmental risk factors must be included as part of the clinical routine prior to transplantation. Regular examination of the skin, instructions on self-monitoring, and the use of protective measures against the sun, are very important for reducing the incidence of skin pathology in transplant patients.

The authors declare no conflicts of interest.

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