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ORIGINAL ARTICLE

Patients with solid organ transplantation and skin cancer: determination of risk factors with emphasis in photoexposure and immunosuppressive regimen. Experience in a third level hospital

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Abstract

Introduction: *Non-melanoma skin cancer (NMSC) is the most common malignancy in transplant recipients. The incidence of basal cell carcinoma (BCC) is 10 times higher than in the general population, whereas that of squamous cell carcinoma (SCC) is 100 times higher. The BCC:SCC ratio is reversed and increases according to the degree of immunosuppression and sun exposure. A method to predict the risk of NMSC should be based on factors such as phototype and total sun burden (TSB).* **Objective:** *To determine the influence of risk factors on the development of NMSC and its relationship with the type and duration of immunosuppresive treatment, type of transplantation and TSB.* **Methods:** *A cohort whereby kidney or liver transplantation recipients were identified was used to record if they developed any form of skin cancer. For the study of the NMSC-associated factors, a case-control study approach was resorted to. Dermatological examination was performed, TSB was calculated and a risk factor questionnaire was applied.* **Results:** *The study enrolled 120 kidney and 20 liver transplant recipients. All NMSC patients (100%) were kidney transplantation recipients. Seventy-eight lesions were found in 40 patients: 59 (76%) corresponded to SCC and 19 (24%), to BCC. The affected zones were: head and neck (60%), trunk (18%) and upper limbs (50%). In 30% (12/40) of the patients, 22 new neoplasms were identified (18 SCC and 4 BCC). In the multivariate analysis, the significant factors were: type of immunosuppressive regimen (odds ratio [OR]: 59.7; 95% confidence interval [CI]: 10.2-248), TSB > 10 points (OR: 19; 95% CI: 3-120) and immunosuppressive treatment duration (OR: 1.06; 95% CI: 0.9-1.1). Mean time from transplantation to first dermatological assessment was 6 years (standard deviation [SD]: +5.4).* **Conclusions:** *Dermatological assessment is convenient and easy to perform. Timely diagnosis and treatment of skin lesions are essential components of a comprehensive evaluation program for transplant recipients.* (Gac Med Mex. 2015;151:19-24)

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Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy in transplant recipients[1]. With regard to the types of NMSC, the incidence of basal cell carcinoma (BCC) is 10 times higher than in the general population, whereas squamous cell carcinoma (SCC) is 100 times more frequent[2]. The usual BCC-SCC ratio is 4:1, which is reversed in transplant recipients, and this reversion increases as the latitude decreases. Therefore, chronic exposure to type B ultraviolet radiation (UVB)

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may be more relevant to the development of SCC than of BCC[3,4]. The increased incidence of NMSC runs paralell to post-transplant survival and, therefore, it represents a particular challenge for dermatologists all over the world. UV radiation (UVR) exposure is thought to be one of the most important environmental risk factors with regard to NMSC and its precursors[5,6]. By interfering with antigen-presenting Langerhans cells, UVR induces tolerance to photo-damaged cells and, therefore, a reduction in immune response to tumor cells. High UVB doses (2 kJ/m^2) can alter the immune response at distance, affecting non-photoexposed sites, which translates into systemic immunosuppression[7-9].

A score to predict individual risk for the development of NMSC over the first 5 years post-transplantation should be based on established risk factors such as phototype (according to Fitzpatrick's classification, it is defined as the sensitivity of the skin to UV light) and determination and quantification of the time of exposure to sunlight, either recreationally or occupationally, by measuring the total sun burden (TSB)[10-12]. The relationship between immunosuppression and the development of melanoma has not yet been established, although an increase in the appearance of melanocitic nevi has been observed in immunosuppressed patients, which might represent an additional risk factor for melanoma[13-15].

Material and methods

Methodological design

The study used an incipient historical cohort; i.e., information was obtained retrolectively by reviewing the active patients' database from the Department of Transplantations of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran (INCMNSZ). All patients that had received a kidney or liver transplantation were identified, recording if, after this event, they had developed any type of skin cancer.

For the study of skin cancer-associated factors, the nested case-control approach was used in the aforementioned historical cohort. In this study, transplant recipients not diagnosed with skin cancer until the time of the study were selected as controls, whereas patients with skin cancer were selected randomly. No matching of any kind was made between cases and controls, since we were interested in finding out the roles of gender, age, time since the transplantation, type of skin, etc., as associated factors. We considered that any kind of matching would lead to an over-matching phenomenon that would hamper the observation of the effect as a risk factor for the variables of interest. Patients were assessed in a single occasion, where any skin neoplasm was disregarded in the controls and the associated risk factors questionnaire was applied in both groups.

Study participants

Patients under the care of the Department of Transplantations from the INCMNSZ who were active during the May 1st 2011 to May 1st 2012 participated in the study.

The inclusion criteria were:

- Alive patients who received a kidney or liver transplantation at the INCMSZ and that signed an informed consent form.

The exclusion criteria were:

- Patients unwilling to participate in the study.
- Unavailability of the medical chart for its review.

Sample size

A total of 140 solid organ transplant recipients were assessed: 40 patients with skin cancer (cases) and 100 without skin cancer (controls) during the stipulated period.

Outcome measures

The primary outcome measure was:

- Presence of skin cancer or not:
  - Type of skin cancer: BCC, SCC or melanoma.
  - Site: topography of the lesion.

Secondary outcome measures were:

- Demographic data: age and gender.
- Total sun burden11 calculated based on:
  - Exposure to 3 factors:
    - Residence in a place with sunny weather = 1, without sunny weather = 0.
    - Occupational sun exposure: never = 0, < 20 h/week = 1, > 20 h/week = 3.
    - Recreational sun exposure: never = 0, < 14 d/y = 1; > 14 d/y = 2.
  - Score addition for 4 periods of life:
    - < 20 years, 20-40 years, 41-60 years, > 60 years.
  - Maximum score of 24.
  - Risk categories:
    - Low: < 6.
    - Moderate-high: 6-10.
    - High: > 10.

Table 1. Patient demographics

Variable	Cancer*	No cancer*	p-value
Age (years)	60	44	< 0.001
Gender			0.82
Female	14 (35%)	37 (37%)	
Male	26 (65%)	63 (63%)	
Phototype			0.48
III	21 (53%)	37 (37%)	
IV	16 (40%)	51 (51%)	

*Data expressed as medians.

- Phototype: defined according to Fitzpatrick's classification as sensitivity of the skin to UV light.
- History of 2 or more painful sunburns: sunburns that have generated discomfort to the patient, especially those involving blisters.
- Use of sunscreen prior and after the transplantation: by means of a standardized questionnaire, by selecting one of three answers: never, some times or always.
- Family history of skin cancer in a close relative (father, mother, sibling).
- Precancerous skin lesions.
- Time elapsed since the transplantation (expressed in years).
- Immunosuppressive treatment regimen: pharmacological group each drug belongs.
- Immunosuppressive treatment duration (expressed in years).

Description of the maneuver

Using a database provided by the Department of Transplantations of the INCMNSZ, patients defined as cases based on the presence of skin cancer and controls due to the absence of skin cancer were selected.

The purposes of the study were explained in detail and an informative and informed consent letter was handed over. After agreeing with the study, the patients underwent a complete examination of the skin through direct observation and with a dermatoscope for any malignancy-suspected lesion. This was carried out in a properly illuminated office and with a nurse present; the patient was asked to remove his/her clothes and to put on an examination gown. Then, a standardized questionnaire on sunlight exposure and risk factors for skin cancer was applied. Complementary data was obtained from the patient chart.

Measurements and statistical analyses

The obtained data were analyzed using descriptive statistical methods to measure central tendency and dispersion (mean, standard deviation, minimum value, maximum value, median, mode), as well as simple frequencies. The IBM® SPSS Statistic® version 19 sofware was used to construct and analyze the databases of the study.

The groups were compared using the chi-square test; a correlation analysis of characteristics demonstrating statistically significant differences was performed by means of uni- and multivariate logistic regression with the odds ratios (ORs) and 95% confidence intervals (CIs) being determined.

Expected biases

Most of the study population lived in Mexico City; therefore, the data may not be generalized to transplant recipients living in other zones of the country.

With regard to the type of immunosuppresive regimen in transplant recipients with skin cancer, the use of sirolimus was under-represented, as it was only included in the treatment of 3 patients, all of them with a history of skin cancer.

Results

Participants

In the period from May 1st 2011 to May 1st 2012, 140 solid organ transplant recipients were included, out of which 100 had received a kidney transplantation and 40 a liver transplantation. During the study, a single dermatological assessment was conducted in the outpatient unit.

Patient demographics

Patient demographics are shown in table 1. Of the 140 patients included, 51 were female and 89, male; 120 were kidney transplantation recipients and 20 liver transplantation recipients. All the patients (100%) who developed NMSC were kidney transplantation recipients. Median age was 49 years. Most patients came from the Distrito Federal. The most common occupations in the patients with cancer included street trade, farmers and motor vehicle drivers.

Table 2. Topography of the skin cancer

Topography	Rate, n (%)
Head and neck	24 (60)
Trunk	7 (17.5)
Upper limbs	20 (50)

Table 3. Skin cancer-associated factors

Variable	Cancer*	No cancer*	p-value
TSB	> 10 points	< 6 points	< 0.001
Immunosuppression time	19 years	8 years	< 0.001
Time to first dermatological assessment	4 years	3 years	< 0.05
Actinic keratoses	16 (40%)	23 (23%)	< 0.05

*Data expressed as medians.

Description of identified neopasms

Seventy-eight NMSC lesions were found in 40 patients: 59 (76%) corresponded to SCC and 19 (24%), to BCC. Of all patients with skin cancer, 45% had more than one lesion. With regard to the location of the NMSC, the most affected zones were those that were photoexposed: head and neck (60%), trunk (18%) and upper limbs (50%) (Table 2). In 30% of the patients (12/40), 22 new neoplasms (18 SCC and 4 BCC) were identified. No lesions consistent with melanoma were identified.

Key results

The groups did not show differences with regard to gender, skin phototype, recreational sun exposure, family history of skin cancer, sunburns or use of sunscreen before and after the transplantation. The results of the comparative analysis between groups using the chi-square test are shown in table 3. In this study, transplant recipients who developed NMSC were shown to be older than patients without NMSC (median age: 60 vs. 44 years). Initially, a univariate logistic regression analisis was conducted, the results of which are shown in table 4. In the multivariate logistic regression analysis (Table 5), the characteristics that maintained statistical significance, in order of strength of association, were the following: type of immunosuppressant regimen based on cyclosporine A, azathioprine (AZA) and prednisone (PDN) (OR: 59.7; 95% CI: 10.2-348), TSB > 10 points (OR: 19; 95% CI: 3-120) and immunosuppressive treatment use duration (OR: 1.06; 95% CI: 0.9-1.1). Noteworthy, 23% (n = 23) of the patients without cancer had premalignant skin lesions (actinic keratoses); in turn, in 40% (n = 16) of the patients with cancer this type of lesions were observed. Mean time from transplantation to first dermatological assessment was 6 years (SD ± 5.4); in addition, 34% (n = 34) of the patients without cancer were assessed for the first time during the study. 93% of the patients did not use sunscreen on a regular basis (never, sometimes) before and after the transplantation. Of the patients with skin neoplasms, 80% had viral warts in photo-exposed sites, predominantly upper limbs.

Table 4. Univariate analysis of risk factors for skin cancer

Variable	OR	95% CI	p-value
Type of immunosuppressive regimen*	29	10.8-78.2	< 0.001
Occupational exposition > 20 h/ week	7.2	2.6-19.6	< 0.01
Immunosuppresion time†	1.18	1.1-1.3	< 0.001
Age‡	1.13	1.08-1.17	< 0.001

*Immunosuppressive regimen: CyA, AZA and PDN.
†Time on immunosuppressive treatment expressed in years.
‡Median ages were compared between the groups with and without cancer.

Table 5. Multivariate analysis of risk factors for skin cancer

Variable	OR	95% CI	p-value
Type of immunosuppressive regimen*	59.7	10.2-348	< 0.001
Occupational exposition > 20 h/ week	19	3-120	< 0.01
Age†	1.16	1.07-1.25	< 0.001
Immunosuppresion time‡	1.06	0.9-1.1	0.1

*Immunosuppressive regimen: CyA, AZA and PDN.
†Median ages were compared between the groups with and without cancer.
‡Time on immunosuppressive treatment expressed in years.

Discussion

All available immunosuppressive drugs cause non-specific immunosuppression and, therefore, they increase the risk of infection and malignancy. Skin cancer is one of the lesions commonly observed after transplantation, and this is why we started a skin cancer screening program. Twenty-two lesions were identified in 12 patients; histological analysis reported 59 SCC and 19 BCC, a 3:1 ratio, which is consistent with reports in the literature[4,11,16].

In the present study, the number of NMSC was significantly higher in the head, neck and limbs than in the trunk. These data confirm the location of NMSC mainly in photo-exposed sites, which strongly indicates that the sun is a factor implicated in the development of these tumors.

Median time from transplantation to first dermatological assessment was 6 years; however, only a periodical examination of the patients carried out since the transplantation will provide accurate data on the time between the procedure and the appearance of skin cancer. Epidemiological and molecular data suggest that NMSC is associated with excessive exposure to UV radiation, especially after transplantation[17]. According to our results, patients with a TSB > 10 points had 19 times higher risk for NMSC, just as reported in other studies[18,19]. Clearly, the TSB was a risk factor associated with NMSC, with occupational exposure being more significant than recreational exposure.

Chemical photoprotection was extremely low in our patients, in spite of existing evidence on its skin neoplasm preventive effect[12,20]. In patients considered to be at risk because of being engaged in continuous outdoors (occupational or recreative) activities, frequent dermatological assessment should be performed (at least once yearly), in addition to insist in avoiding prolongued sun exposure in order to promote skin cancer primary prevention.

Noteworthy, a high percentage of patients were assessed by a dermatologist for the first time during the study, which implies an awareness of the medical personnel on the importance of both premalignant and malignant lesions detection, soon after the transplantation or, ideally, before the procedure. Based on all of this, we propose dermatological assessment to be included as part of the solid organ transplantation protocol, prior and after the procedure, with the latter at least once yearly.

Other important factor in the post-transplant development of neoplasms is the immunosuppressive treatment. Several immunosuppressive agents can accelerate the development of NMSC in this group of patients by means of two mechanisms: first, these drugs can be directly carcinogenic, and second, chronic immunosuppression alters immunosurveillance and erradication of premalign changes. A number of prospective studies have confirmed the carcinogenic effect of calcineurin inhibitors[6,21].

According to our experience, the rate was significantly higher in patients treated with CyA and AZA. These agents can increase the production of growth factors during tumor progression.

In a restrospective study conducted by Gómez-Roel et al. at the INCMNSZ[22], the most common malignancies documented in kidney transplantation recipients were NMSC and lymphomas; the most common immunosuppressive treatment was based on CyA and AZA.

No melanoma-type lesions were observed in this study, which could be explained by the small sample size and, in addition, because the incidence of this neoplasm is lower tan that of NMSC.

Limitations

No information could be obtained regarding the latency between the transplantation and the apperance of NMSC, as routine follow-up for identification of malignant lesions has not been carried out in these patients.

Generalization of results

The information obtained in this study is not representative of transplant recipients from other geographic zones of the country.

Conclusions

In conclusion, NMSC represents the most common malignancy in transplant recipients, which confers them significant morbidity and mortality. Dermatological assessment is simple and easy to implement, in addition to being highly accepted by the patients. Intensive education, primary prevention, early intervention and close follw-up are key components of a skin neoplasms early detection program in order to reduce associated complications in solid organ transplantation recipients.

The risk factors for the development of NMSC identified in transplant recipients were the type immunosuppressive treatment being based on CyA, AZA and PDN, TSN > 10 and immunosuppressive treatment duration.

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