Skin disorders in renal transplant recipients: a retrospective study*

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20176040

Abstract: Background: Immunosuppressive therapy, which is necessary to avoid graft rejection in renal transplant recipients, presents an increased risk of several pathologies, namely infectious and neoplastic.
Objectives: To identify the most frequent skin diseases and their clinical and demographical risk factors within a population of renal transplant recipients.
Methods: A retrospective study of renal transplant recipients referred to dermatology visit and observed for the first time from January 2008 to December 2014.
Results: The study included 197 patients, 120 men (60,9%). Mean age was 50,7 years (±13,4). 12 patients (6,1%) had previous skin cancer. Infections were the most frequent reason of referral (93/197; 44%). From the total referred, 18,3% (36/197) presented pre-cancerous lesions. Malignancy was diagnosed in 36 patients (18,3%), with 29 non-melanoma skin cancers (14,7%) and 7 Kaposi sarcomas (3,6%). Ratio of basal cell carcinoma to squamous cell carcinoma was 1,1:1. Non-melanoma skin cancer was significantly associated with older age (p = 0,002), male gender (p = 0,028), history of previous skin cancer (p = 0,002) and higher duration of immunosuppressive therapy (p<0,001).
Study limitations: Retrospective study, with data from the first visit in dermatology. We didn't made classification on skin-types.
Conclusions: The great incidence of cutaneous infections and skin cancer is responsible for a significant morbidity. It is important to assure the regular dermatological follow-up of renal transplant recipients, which will promote the prevention, an early diagnosis and an efficient treatment.
Keywords: Carcinoma, basal cell; Carcinoma, squamous cell; Kidney transplantation; Skin neoplasms

INTRODUCTION

In renal transplant, the use of immunosuppressive drugs, indispensable to avoid organ rejection, implies an increased risk of several infectious and neoplastic diseases.[1]

Cutaneous infections have a very high incidence in patients submitted to renal transplant and are diagnosed in 55-97% of these individuals.[2]

The incidence of cutaneous neoplasia, particularly of non-melanoma skin cancer, is well characterized, with an increased risk of 20-times in the case of basal cell carcinoma (BCC) and 65-times in the case of squamous cell carcinoma (SCC).[3,4] Cutaneous neoplasms appear at an earlier age and have a more aggressive behavior, with greater local invasiveness and a greater tendency to metastasize.[4,5]

Knowledge on the spectrum of skin diseases that most frequently affects patients undergoing renal transplant, in particular the understanding of their clinical presentation and their severity, is fundamental to elaborate dermatological follow-up plans in order to enhance their quality of life and increase their longevity.

The objectives of this study were to characterize a series of patients undergoing kidney transplantation and to identify the most frequent skin diseases when referring to the dermatology clinic. We also aimed to identify sociodemographic and clinical risk factors for diagnosed cutaneous neoplasms.

METHODS

We performed a retrospective study, including 223 patients who underwent renal transplant after 1979, referred to the specialist consultation on Dermatology for Transplanted Patients between January 2008 and December 2014. In that period, a total of 1,070 dermatology consultations were performed for transplanted patients, 223 were first-time consultations and 847 were subsequent consultations.

The sample is of convenience and is not representative of the population of renal transplant patients in Portugal. All patients aged <16 years (n = 1) and those who underwent bone marrow transplantation (n = 2) or liver transplantation (n = 5) were excluded. Those who were maintained on hemodialysis after transplant rejection (n = 2) or who were waiting for transplantation (n = 16) at the time of the first visit were also excluded. From the initial convenience sample, 26 patients were excluded, totaling 197 eligible patients for the study.

Data were obtained by reviewing the records of the first consultation performed, after referral. All neoplasm diagnoses had

Received on 15.05.2016.
Approved by the Advisory Board and accepted for publication on 07.07.2016.
* Study conducted at Unidade de Investigacao em Dermatologia, Faculdade de Medicina da Universidade de Lisboa and Clinica Dermatologica da Universidade de Lisboa, Centro Hospitalar Lisboa Norte, EPE (CHLN) – Lisbon, Portugal.
Financial support: None.
Conflict of interest: None.

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histological confirmation. Duration of immunosuppressive therapy was estimated from the date of transplantation to the date of the specialty visit.

Statistical analysis was performed using SPSS® software (Statistical package for the social sciences, version 18, SPSS Inc, Chicago, IL, USA), with significance level of 5%. Non-parametric Mann-Whitney test and chi-square test were used, with Cramer's V as a measure of association. Fisher's exact test was also used when any of the expected frequencies was less than five.

RESULTS

In this study, 197 renal transplant patients were included, 120 were men (60.9%) and 77 women (39.1%).

Patients' age at the time of the first consultation, after referral, ranged from 19 to 79 years, with a mean of 50.7 years and a median of 54 years (± 13.4 years).

Of the 197 patients in the sample, 167 were Portuguese (84.8%), 12 were Angolan (6.1%), 9 were Cape Verdean (4.6%), 4 were native from Guinea- Bissau (2.0%), 3 from São Tomé and Príncipe (1.5%), 1 from Moldova (0.5%) and 1 from England (0.5%).

Regarding race, 169 patients were Caucasian, Fitzpatrick I-IV phototype (85.8%) and 28 non-Caucasian, Fitzpatrick V-VI phototype, (14.2%).

The time elapsed since the transplant varied between one and 384 months, with a mean of 89.5 months and a median of 72 months (± 79.9 months).

A history of previous cutaneous neoplasia was found in 12 patients (6.1%), with 7 BCC (3,5%), 4 SCC (2,0%), 1 Kaposi's sarcoma (0,5%), and 1 Bowen's disease (0,5%). In one patient, the diagnosis of BCC and SCC coexisted.

Previous history of non-melanoma skin cancer was significantly associated with longer immunosuppression (MW: U = 271.0; p <0.001).

Maintenance immunosuppressive schemes for organ rejection prevention were variable, being composed of drugs of four therapeutic classes: corticosteroids (prednisolone), antiproliferative agents (azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporine and tacrolimus), and mTOR protein kinase inhibitors (sirolimus and everolimus). A total of 144 patients (73.1%) were maintained in a three-drug regimen. Drugs used in the study sample are specified in table 1.

In 37 patients (18.8%), pre-neoplastic lesion or SCC *in situ* was diagnosed, with 27 cases of actinic keratosis (13.7%), 7 cases of Bowen's disease (3.6%), 3 cases of keratoacanthoma (1.5%), and 1 case of actinic cheilitis (0.5%). In one patient, simultaneous presence of actinic keratosis and Bowen's disease was observed.

In this study, actinic keratosis was significantly associated with greater age (MW: U = 1014.5; p <0.001), higher period of immunosuppression (MW: U = 1250.0, p <0.001), azathioprine therapy (p = 0.047, V = 0.16) and with previous cutaneous neoplasia (p = 0.015, V = 0.27).

Diagnosis of neoplasia was confirmed histologically in 36 patients (18.3%). There were 29 cases of non-melanoma skin cancer (14.7%) and 7 cases of Kaposi's sarcoma (3.6%). Of the 29 cases of non-melanoma skin cancer (14.7%), 16 were BCC (8.1%) and 15 were SCC (7.6%), with both diagnoses coexisting in two patients.

All cases of Kaposi's sarcoma were diagnosed in non-Caucasians, and no non-melanoma skin cancer or pre-neoplastic lesion was diagnosed in these patients.

Non-melanoma skin cancer was significantly associated with age (MW: U = 1561.5, p = 0.002), male gender (p = 0.028, V = 0.16) and with previous cutaneous neoplasia (p = 0.002, V = 0.31). Regarding the influence of therapy, a higher incidence was observed with the longer duration of immunosuppression (MW: U = 1236.0; p <0.001). In the isolated analysis of patients with BCC, only the association with a longer immunosuppression period remained statistically significant (MW: U = 803.5, p = 0.003). Concerning the isolated evaluation of SCC, associations with greater age (MW: U = 721.5, p = 0.002) and history of cutaneous neoplasia (p = 0.006; = 0.29) remained significant. Longer duration of immunosuppressive therapy (MW: U = 708.5; p = 0.002) significantly increased the incidence of this neoplasm.

Viral infections were diagnosed in 46 patients (23.4%). These are listed in table 2. Viral infection was significantly associated with azathioprine-containing immunosuppressive regimens (p <0.001, V = 0.399).

Diagnosis of fungal infection was made in 37 patients (18.8%), with 17 cases of dermatophytosis (8.6%), 15 of pityriasis versicolor (7.6%), five of pityrosporum folliculitis (2.5%), and two of candidiasis (1.0%). In one patient, the simultaneous diagnosis of dermatophytosis and candidiasis was made and, in another, dermatophytosis and pityriasis versicolor.

Bacterial infections were present in 10 patients (5.1%), as described in table 3.

Benign cutaneous tumors were observed as a reason for consultation in 31 patients (15.7%).

The diagnosis of inflammatory dermatosis was made in 23 patients (11.2%), and the pathologies observed are specified in table 4.

In six patients, an adverse drug reaction (3.0%) was observed, with 3 cases of acneiform eruption resulting from taking cor-

Table 1: Immunosuppressive therapy in the study sample

Drugs	Frequencies	
Prednisolone	87.3%	172/197
Mycophenolate mofetil	82.7%	163/197
Tacrolimus	48.2%	95/197
Cyclosporine	41.1%	81/197
Sirolimus	7.1%	14/197
Azathioprine	5.6%	11/197
Everolimus	0.5%	1/197

Table 2: Viral infections

Diagnosis	Frequencies	
Viral non-genital warts	15.7%	31/197
Genital condylomas	3.1%	6/197
Non-genital herpes infection	2.0%	4/197
Genital herpes	1.0%	2/197
Molluscum contagiosum	1.0%	2/197
Herpes zoster	0.5%	1/197

ticosteroids (1.5%), 1 case of mouth ulcer (0.5%), 1 case of purpura (0.5%) and 1 case of toxin to tacrolimus (0.5%).

In 25 patients, other dermatological conditions were diagnosed, not groupable in the previously specified categories (12.7%).

DISCUSSION

The present study allowed the characterization of the spectrum of skin diseases that motivated the referral to the Dermatology Clinic of Hospital Santa Maria in a series of renal transplant patients.

The main limitations of this study arise from the fact that this is a retrospective study, with data obtained through the analysis of records, and the fact that the sample is of convenience and therefore not representative of the population of patients undergoing renal transplant in Portugal, limiting the possibility of generalization of the results obtained. Although it is an important risk factor for non-melanoma skin cancer, it was not possible to classify the individuals enrolled into phototypes. Results of diseases diagnosed in this study correspond to the frequency observed as a reason for referral to the dermatology clinic, and it is not possible to guarantee that they correspond to the true prevalence of this population. Data included in this study refer only to the first consultation performed in the dermatology specialty, after referral, which makes it difficult to correctly characterize the spectrum of diseases presented over time. Some diseases of cutaneous nature may have been treated either by the transplant team or by other specialists in an outpatient setting, a fact that may have led to underreporting.

The most frequent etiology of the diseases that led to this consultation was infectious (44%). There was a predominance of viral infections (23.4%), mainly caused by the human papilloma virus and the herpes virus. Fungal infections appeared as the second more frequent (18.8%) and bacterial infections as the ones with the lower incidence (5.1%). These results differ from those obtained by Fernandes, S. *et al.*, [6] with a sample composed of renal and hepatic transplant patients, in which fungal infections were the most observed (20.5%), followed by viral (12.7%) and bacterial (8.5%). They also differ from the data presented in the study of Wisgerhof HC. *et al.*, [2] in which, in a series composed of patients undergoing renal and/or pancreatic transplant, bacterial infections, followed by viral and, finally, fungal infections, were more frequent. However, despite the disparity in the type of the most frequent causative microorganism, both corroborate the infectious etiology as the main reason for the use of dermatology consultation in the population composed of renal transplant patients.

Table 3: Bacterial infections

Diagnosis	Frequencies	
Folliculitis	1.5%	3/197
Boil	1.0%	2/197
Impetigo	0.5%	1/197
Abscess	0.5%	1/197
Cellulitis	0.5%	1/197
Paronychia	0.5%	1/197
Bacterial superinfection of herpetic lesions	0.5%	1/197

Table 4: Inflammatory dermatoses

Diagnosis	Frequencies	
Seborrheic dermatitis	7.6%	15/197
Eczema	2.0%	4/197
Psoriasis	0.5%	1/197
Irritant contact dermatitis	0.5%	1/197
Perioral dermatitis	0.5%	1/197

In this study, therapy with regimens that included azathioprine was significantly associated with a higher incidence of viral infection. It is possible that this drug induces a more marked depletion in the number and function of Langerhans cells, a fact that justifies the relationship described and already verified in previous studies.[7,8]

In renal transplant patients, infections tend to have a more severe course, with a more rapid and more intense progression, generating abnormally severe and sometimes atypical conditions.[1,9] Thus, knowledge on the spectrum of the various forms of clinical presentation plays a pivotal role for early diagnosis and appropriate therapy. It may also be necessary to use preventive therapies, namely drugs and vaccines used prophylactically.[6]

In this study, non-melanoma skin cancer accounted for 14.7% of referrals to the dermatology clinic. This value is similar to that obtained by Fernandes, S. *et al.*, who, in a sample of renal transplant recipients, recorded an incidence of 13.3% of this neoplasm.[6] In the present series, non-melanoma skin cancer was significantly associated with age, male gender, longer duration of immunosuppressive therapy, and with previous cutaneous neoplasia.

In general population, a ratio of 4:1 between BCC and SCC is reported. In the transplanted patients, with time, there seems to be an exponential growth in incidence of SCC and a linear growth of BCC, so that the inversion of the ratio described is observed.[10] In this study, no such inversion was observed, with the number of BCC being greater than that of SCC, reaching a ratio of 1.1:1. This fact is in agreement with the data present in other studies conducted in the Mediterranean region, in which there seems not to be the typical inversion of the Anglo-Saxon and Scandinavian countries, probably due to genetic differences and sun exposure habits.[11,12,13]

Although there is an increased risk of melanoma in the population of renal transplant patients by 1.6 to 3.4 times in the European territory, [4] in this series, there was no diagnosis of any case of this neoplasia.

Pre-neoplastic lesions were also an important reason for consultation in this study (18.8%), especially actinic keratosis, responsible for 13.7% of the referrals. This value differs from others from studies conducted in the Portuguese population. On the one hand, it is superior to data from the study of Fernandes, S. *et al.*, in which the incidence of this pathology was 5% in renal transplant patients[6] and it is, on the other hand, lower than those obtained by Borges-Costa, J. *et al.*, whose value obtained was 24%.[12] In the present study, actinic keratosis was significantly associated with greater age, longer immunosuppression, azatoprine therapy and presence of history of cutaneous neoplasia. The risk of progression to malignant disease, which is proportional to the actinic damage, and the positive relationship between previous cutaneous neoplasia and the

risk of developing non-melanoma skin cancer, clearly highlight the importance of identifying and treating these patients.[14]

The fact that cutaneous neoplasia develops at earlier ages, with increased incidence, increased local aggressiveness and increased risk of metastasis[4,10] implies the need to adopt preventive strategies. All patients undergoing renal transplant should receive information on the increased risk of this neoplasm and the importance of photoprotection measures before and after surgical intervention.[4,15] It is essential to ensure a good dialogue between the specialty of dermatology and the transplant team. It is also important to develop an adequate follow-up program, created from a risk stratification,[4] always by means of a medical evaluation, performed, preferably, on transplant candidates.

Inflammatory dermatoses were frequently diagnosed in this series (11.2%). Seborrheic dermatitis was the most prevalent diagnosis (15/197, 7.6%). This value is close to that obtained by Lally, A. *et al.* (9.5%) [16] and confirms the higher incidence of this disease in patients submitted to renal transplant, already identified in previous studies.[16] It should also be highlighted the interaction of immunosuppressive therapy with some of the diagnoses included in the group of inflammatory dermatoses, namely psoriasis and eczema, in which these drugs are used for therapeutic purposes, thus explaining their low incidence.[16]

In this series, adverse drug reactions accounted for only 3.0% of referrals to the dermatology specialty. This value is significantly lower than that recorded in the study of Fernandes, S. *et al.* (8.3% in the group of patients undergoing renal transplant) [6] and than that obtained in the study by Lally, A. *et al.*, in which, although there was no total quantification of cutaneous lesions of iatrogenic nature, considerably higher values of some adverse drug reactions were observed, such as purpura (41%) and gingival hyperplasia (27%).[16] The lower reference rate observed in Portuguese studies, particularly in this series, may be the result of the effective treatment of these lesions by transplant teams, rather than a lower rate of occurrence.[6]

The present study made it possible to emphasize the high prevalence of skin diseases in patients undergoing renal transplant. These lesions have a strong impact on the quality of life of these patients, which may contribute to lower adherence to immunosuppressive therapy.[16] As such, it is important to recognize it and treat it properly and early, preferably in specialized centers.

CONCLUSION

The progressive increase in the longevity of patients undergoing renal transplant has modified the spectrum of skin diseases, making them therapeutic challenges of increasing complexity. The high incidence of lesions of a benign nature, namely infections, with strong impact on quality of life, and of cutaneous neoplasias, with associated morbidity, places particular relevance in the specialty of dermatology in the treatment of these patients. It is therefore crucial to ensure appropriate follow-up, with periodic evaluations from the pre-transplant stage. The main aim is ensure adherence to strategies to prevent skin cancer, promote early diagnosis and the effective treatment of various skin conditions. ❑

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How to cite this article: Garrido PM, Borges-Costa J. Skin disorders in renal transplant recipients: a retrospective study. An Bras Dermatol. 2017;92(5):638-41.