

Most frequent dermatosis in patients with kidney transplantation

Dermatosis más frecuentes en pacientes con trasplante renal

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Abstract

Objective: To determine the most frequent dermatoses in patients with kidney transplant in the dermatology consultation, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, in Mexico City, in the period from March 2016 to March 2020. **Method:** Descriptive, cross-sectional study that included 153 patients with a complete medical history with prior informed consent and authorization from the hospital ethics committee. **Results:** All patients presented one or more dermatoses. The most frequent were infectious (mycosis, viral) and, in decreasing order, other dermatoses (keratosis pilaris, melasma), tumorous (benign), inflammatory (seborrheic dermatitis, eczema), probably secondary to drugs and autoimmune (alopecia areata). **Conclusions:** All kidney transplant patients presented at least one dermatosis, predominantly those of infectious origin. We recommend dermatological evaluation prior to transplantation for timely diagnosis and treatment of dermatoses that could increase the morbi-mortality of patients.

Keywords: Dermatitis. Kidney transplant. Chronic kidney disease.

Resumen

Objetivo: Determinar las dermatosis más frecuentes en pacientes con trasplante renal en la consulta de dermatología del Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, en Ciudad de México, en el periodo de marzo de 2016 a marzo de 2020. **Método:** Estudio descriptivo, transversal que incluyó 153 pacientes con historia clínica completa, previo consentimiento informado y autorización del comité de ética del hospital. **Resultados:** Todos los pacientes presentaron una o más dermatosis. Las más frecuentes fueron las infecciosas (micosis, virales) y, en orden decreciente, otras dermatosis (queratosis pilar, melasma), tumorales (benignas), inflamatorias (dermatitis seborreica, eccemas), probablemente secundarias a fármacos y autoinmunitarias (alopecia areata). **Conclusiones:** Todos los pacientes receptores de trasplante renal presentaron al menos una dermatosis, predominando las de origen infeccioso. Recomendamos una valoración dermatológica previa al trasplante para el diagnóstico y el tratamiento oportuno de las dermatosis que podrían aumentar la morbimortalidad de los pacientes.

Palabras clave: Dermatitis. Trasplante renal. Enfermedad renal crónica.

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Introduction

Kidney transplant is the replacement therapy of choice in most patients with advanced stage chronic kidney disease. Successful transplant is associated with improved survival, improved quality of life and, undoubtedly, a significant decrease in healthcare costs compared to any dialysis modality¹.

Kidney transplant patients have an increased risk of developing skin diseases associated with their own immunosuppression and the adverse effects of immunosuppressive treatments². Immunosuppressive therapy received by the kidney transplant patient generally suppresses immunity against bacteria, fungi, and even tumors³. The prevalence of dermatoses in kidney transplant patients is above 70%^{2,4-6}, and in the largest Polish series by Imko-Walczyk et al.⁷, it is 98%.

In 2016, Unal² conducted a review of articles on skin lesions following kidney transplant. He found wound infections one month after transplant, reactivation of herpes in the first week, infections by opportunistic microorganisms in the second and fifth month, and viral and fungal infections at 6 months after transplant. Squamous cell carcinoma is the most common carcinoma in kidney transplant patients and is associated with human papillomavirus (HPV) infection and actinic keratoses².

In this context, the aim of the present study was to determine the most frequent dermatoses in kidney transplant patients in the dermatology outpatient clinic of the Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social (IMSS), Mexico City, in the period from March 2016 to March 2020.

Method

Patients with a history of kidney transplant were included. Each patient was invited to participate freely and, in case of acceptance, signed an informed consent form approved by the local ethics and research committee of the Hospital de Especialidades, Centro Médico Nacional Siglo XXI, IMSS. The data collection sheet was assigned a page number to protect patient privacy and included name, sex and age, medical history, date of transplant, cause of kidney disease, type of donor, immunosuppressive treatment, and dermatologic diagnosis. A complete physical examination of the skin, hair, and nails was performed. If necessary, and with prior signature on informed consent, samples were taken for direct examination or culture of fungi

and bacteria, laboratory and office tests, or skin biopsy. Subsequently, the clinical dermatologic diagnosis was recorded. Treatment was provided where needed and a follow-up appointment was scheduled.

The dermatoses detected in the patients were analyzed and classified into 6 groups: infectious, autoimmune, inflammatory, tumors, probably secondary to drugs, and other dermatoses (those that did not fit into a described group). The frequency of dermatoses according to age, sex, comorbidity, cause of kidney disease, type of donor, date of transplant, and immunosuppressive treatment was analyzed. We determined whether there was an association with these variables or not.

The immunosuppressive therapy the patient was receiving was classified into 5 groups: 1) tacrolimus, azathioprine, and prednisone; 2) tacrolimus, mycophenolate, and prednisone; 3) cyclosporine, mycophenolate, and prednisone; 4) sirolimus, prednisone, and mycophenolate; and 5) others.

The dermatoses were classified into 5 groups according to the time of progress, either before or after kidney transplant, as follows: 1) dermatosis prior to kidney transplant; 2) 1 day to 1 year post kidney transplant; 3) 1 year and 1 day to 5 years post kidney transplant; 4) 5 years and 1 day to 10 years post kidney transplant; and 5) more than 10 years and 1 day post kidney transplant.

The statistics were descriptive, and the analysis was expressed with measures of central tendency and dispersion depending on the type of variable.

Results

A total of 180 patients were reviewed, of whom 27 were on protocol for first or second kidney transplant, and 153 met the selection criteria, 88 men (58%) and 65 women. The average age was 37.3 years (maximum 74 years old and minimum 18 years old). The most frequent CKD etiology was "undetermined" (Fig. 1). The predominant comorbidity was arterial hypertension (Fig. 2). The most frequent type of donation was living related donor in 114 (75%) cases and cadaveric donor in 39. According to the treatment, the drugs used were divided into 5 groups. The most used group of drugs was tacrolimus, prednisone, and mycophenolate, in 95 patients (Fig. 3).

All patients presented one or more dermatoses. A total of 54 different dermatoses were identified and divided into 6 groups. The most common dermatoses

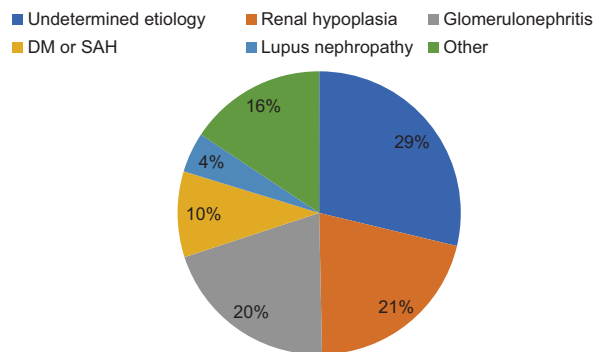


Figure 1. Etiology of kidney disease. DM: diabetes mellitus; SAH: systemic arterial hypertension.

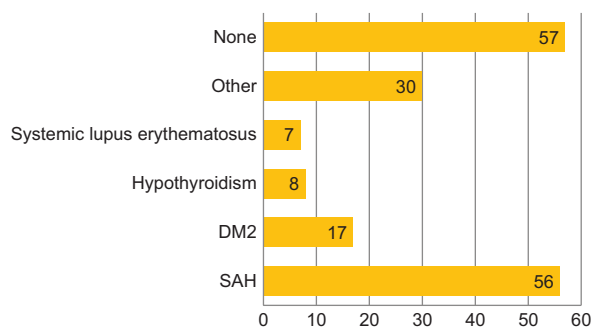


Figure 2. Comorbidity of kidney transplant patients. DM2: type 2 diabetes mellitus; SAH: systemic arterial hypertension.

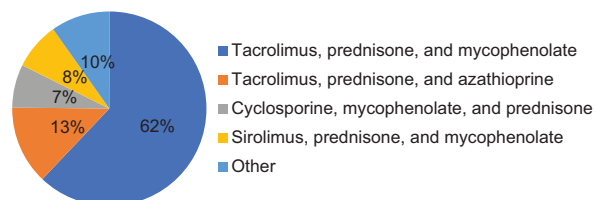


Figure 3. Immunosuppressive treatment.

were those of infectious origin (Fig. 4) and were classified into 4 groups according to the causative agent: fungi, bacteria, viruses, and parasites. The most common were those caused by fungi and viruses, each with 5 different dermatoses, followed by those caused by bacteria, with 3 cases, and by parasites, with 2 cases. Onychomycosis occurred in 33 patients (21.5%) (Fig. 5), hypochromic pityriasis versicolor in 14 patients and hyperchromic variety in 8 patients (Fig. 6); subsequently, tinea, and of these, tinea pedis in 8 patients,

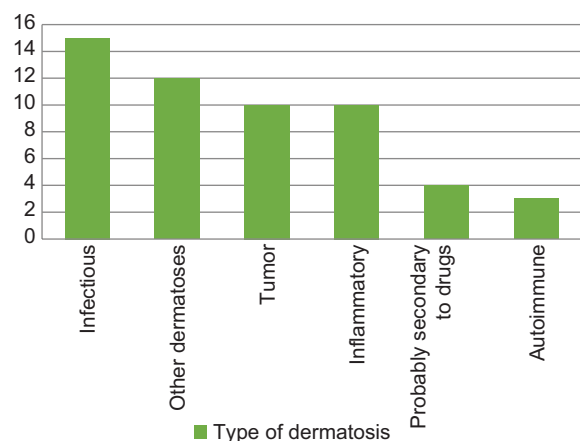


Figure 4. Groups of dermatoses.



Figure 5. Patient with kidney transplant and foot onychomycosis. A: dermatosis located in 10 toenails with different degrees of pachonychia, onycholysis, and xanthonychia. B: close-up of the nail of the first toe of the left foot.

tinea corporis in 3 patients, and tinea incognito and tinea cruris in 1 patient each. Of the dermatoses caused by viruses, warts caused by HPV, in their flat, common, plantar, and genital varieties, occurred in 43 patients, followed by molluscum contagiosum in 8 patients, herpes zoster in 7 patients (Fig. 7), and finally, chickenpox and herpes simplex with 1 patient each. Of the infectious dermatoses caused by bacteria, folliculitis predominated in 5 patients and folliculitis decalvans in 1 patient. In addition, there were *pitted* keratolysis and erythrasma in 1 patient each. Of the infectious dermatoses caused by parasites, demodicosis was found in 3 patients (Fig. 8), and scabies in 2 patients. Dermatoses of autoimmune origin had a low frequency: 6 patients with alopecia areata, 1 with deep lupus, and 1 with vitiligo. As for inflammatory-type dermatoses, there were 10 variants; of these, seborrheic dermatitis was the most common, occurring in 6 patients (Fig. 9). The group of tumor dermatoses was divided into benign, premalignant, and malignant tumors. Benign tumors predominated in 12 patients,



Figure 6. Patient with kidney transplant and hyperchromic pityriasis versicolor. Dermatitis located in the trunk characterized by erythematous, pigmented, nummular plaques of different sizes, with positive Besnier's sign.

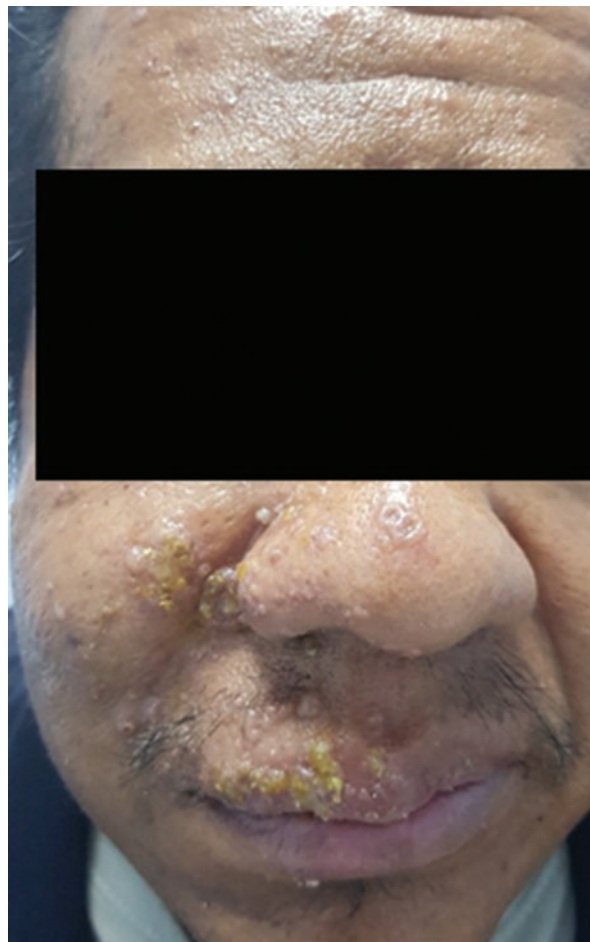


Figure 7. Patient with kidney transplant and herpes zoster involving the mandibular branch of the right trigeminal nerve. It is characterized by grouped vesicles and honey-colored crusts on an erythematous base.

including seborrheic keratoses and cysts; secondly, malignant tumors in 8 patients (Fig. 10), and finally, premalignant tumors in 2 patients. Dermatoses in the probably secondary to drug use group were found in 29 patients: acneform dermatitis in 10 patients, steroid-exacerbated acne in 9 patients, sebaceous hyperplasia in 6 patients, and diffuse alopecia in 4 patients. The second most frequent group of dermatoses was the one labelled “other dermatoses”; most of them were present in only 1 patient.

As for the time of transplant, there were 14 dermatosis variants prior to kidney transplant. The most frequent ones were onychomycosis, HPV warts in all their varieties, seborrheic dermatitis, melasma, and acne. The greatest variety of dermatoses was found in the period from 1 day to 1 year after kidney transplant, with a total of 32 dermatoses (Fig. 11). In the period from 1 year and 1 day to 5 years after kidney transplant, 28 different types of dermatoses were detected. As in the previous period, pityriasis versicolor in its hyperchromic and hypochromic varieties, together with HPV warts in all their varieties, came first, followed by onychomycosis, alopecia areata, molluscum contagiosum, tinea, herpes zoster, seborrheic

dermatitis, sebaceous hyperplasia, and urticaria. The dermatoses found in the period from 5 years and 1 day to 10 years after kidney transplant were of 16 types; the most frequent five were onychomycosis, HPV warts, molluscum contagiosum, pityriasis versicolor, and herpes zoster. Finally, the dermatoses found more than 10 years after transplant were of 16 types; in descending order, HPV warts, onychomycosis, squamous cell carcinoma, tinea, and herpes zoster.

Discussion

Successful kidney transplant is associated with increased survival, improved quality of life, and decreased healthcare costs¹. However, dermatoses have been reported in transplant recipients that may compromise the life of the patient with a functional transplanted



Figure 8. Patient with kidney transplant, demodicidosis, and moderate papulo-telangiectatic rosacea. Dermatoses located on the cheeks characterized by erythematous papules and papulo-vesicles with horny plug.

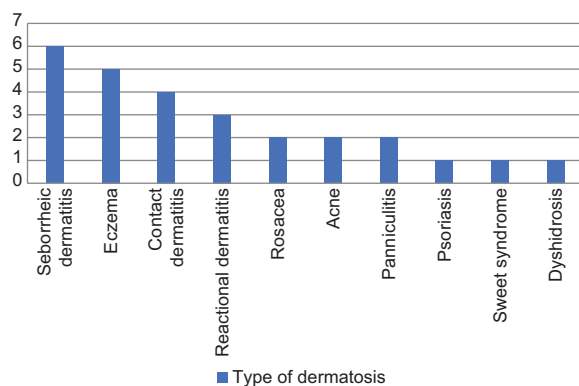


Figure 9. Inflammatory dermatoses.

kidney. The prevalence of dermatoses in these patients varies, according to different publications, between 55% and 98%^{4,7,8}. In our study we report a 100% prevalence of dermatoses associated with or independent of kidney transplant.

Most studies include in their classification infectious, malignant, and premalignant dermatoses^{2,5-7,9}, and occasionally inflammatory⁸. In our study we extend the classification as follows: 1) infectious with 4 categories (viral, fungal, bacterial, and parasitic); 2) autoimmune; 3) inflammatory; 4) tumors (benign, premalignant, and malignant); 5) probably associated with drugs; and 6) other dermatoses. Likewise, the registry was made according to the time of presentation: the first group was the one that presented dermatosis prior to transplant, group 2 in the first year



Figure 10. Patient with kidney transplant and squamous cell carcinoma. Dermatoses located in the right orbito-temporal region. It is characterized by a plaque of 5 × 6 cm in its largest diameters, with poorly defined borders, consisting of sclerosis, atrophy, and ulceration of 1 cm with serosanguineous exudate.

after transplant, group 3 from the first year to 5 years, group 4 from 5 to 10 years, and group 5 more than 10 years after transplant. This allowed us to identify the following: transplant was more frequent in men (58%), as reported by Formicone et al.⁸ in their study. The average age at the time of transplant was 37.3 years, similar to that found in another Mexican study by Magaña et al.¹⁰ and at an earlier stage than in the study by Lima et al.⁹ in Brazil.

In our study, fungal and viral infections were the most frequent, as previously reported⁶. In addition, according to the timing of transplant, dermatoses developed by skin infections have been observed in the first post-transplant months, specifically in the first 7 months⁸. We report 63 cases of superficial mycoses, with a prevalence of 45%, which is higher than that reported by Magaña et al.¹⁰ in Mexico in 2013 of 36%, and by

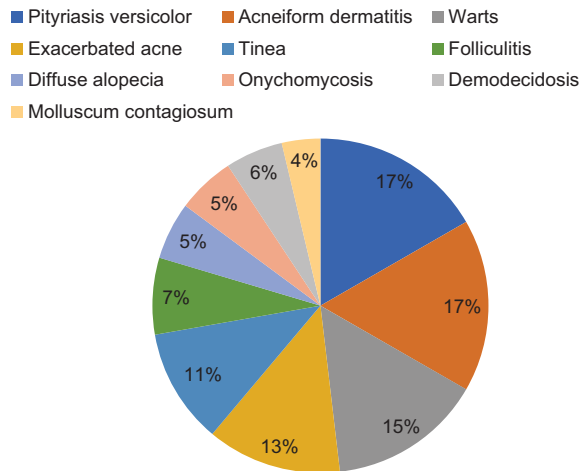


Figure 11. Dermatitis in the group from 1 day to 1 year after kidney transplant.

Sentamil et al.¹¹ in India in 1999 of 42%. As in the latter study, the most frequent causative agent was *Trichophyton rubrum*.

Onychomycosis was more frequent as a dermatosis prior to kidney transplant, and subsequently in those patients between 1 and 5 years after kidney transplant. Pityriasis versicolor was more common in patients classified between 1 and 5 years after kidney transplant and subsequently in those with 1 day to 1 year after kidney transplant. These results are similar to those published by Unal². Viral infections ranked second. Warts due to HPV infection, including flat, common, plantar, and genital varieties, occurred in 43 patients, with a prevalence of 28.1%, compared to 17.5% in the study by Formicone et al.⁸ and 18.4% in the study by Imko-Walczyk et al.⁷.

The incidence of non-melanoma skin cancer increases with the level of immunosuppression. The incidence in kidney transplant patients ranges from 10% to 43% within the first 10 years after transplant and from 40% to 80% after 20 years⁸. In our study, tumor lesions were divided into benign, premalignant, and malignant. The most frequent were benign (seborrheic keratoses and cysts), followed by malignant with 8 cases of squamous cell carcinoma, which is why these patients should be followed up, since it has been reported that squamous cell carcinoma is more aggressive and has a higher mortality rate in kidney transplant patients². The study by Sandoval et al.¹² conducted in Chile reports a prevalence of actinic keratoses of 17%. In our study they were found with low prevalence, as they were only detected in 2 patients, thus representing the least frequent tumor dermatosis.

Of the dermatoses of inflammatory etiology there were 10 variants. Seborrheic dermatitis was the most common with 6 cases, followed by eczema with 5 cases. Morales et al.⁴ report a prevalence of 12.1% for seborrheic dermatitis, in contrast to 3.9% in our study.

Dermatoses of autoimmune origin had a low prevalence in our study, with only 8 patients, 6 of them with alopecia areata. We have no point of comparison in the reviewed studies. However, we consider of great interest to follow up these patients—since alopecia areata is an autoimmune disease— and how to explain its expression in immunosuppressed patients. This and its relationship with transplant recipients are points to be clarified in the future, since it has been described that the transplanted kidney may share antigenic determinants with the hair follicle¹³.

Regarding the association with prolonged use of immunosuppressants, hypertrichosis, gingival enlargement, acne, and striae have been reported³. In our study, acneiform dermatitis predominated in 10 patients, steroid-exacerbated acne in 9 patients, sebaceous hyperplasias in 6 patients, and diffuse alopecia in 4 patients. Most of the observed effects were attributed to the systemic steroid, but sebaceous hyperplasia and diffuse alopecia have been associated with cyclosporine use. Imko-Walczyk et al.⁷ reported a 60% prevalence of hypertrichosis in kidney transplant patients; for purpura it was of 50.2%, for steroid-exacerbated acne 40%, for xerosis 41.2%, and for gingival enlargement 28.2%.

In the group of other dermatoses, the most frequent one was keratosis pilaris in 4 patients, followed by melasma in 3 patients. Morales et al.⁴ reported, within their group of “other dermatoses”, onychodystrophy in 9% of patients in the *hallux*. However, they found no involvement of the fingernails or clinical signs of half and half nail.

In our study we found an increase in fungal and viral infections in the first months after transplant. Most infections were pityriasis versicolor and HPV warts. However, contrary to what is published in the literature, in our study we had patients with herpes simplex and herpes zoster more frequently in the group 1 to 5 years after transplant, and not before, as reported by Unal² in his review.

In the group of 10 years after kidney transplant, it is important to mention the increase in non-melanoma skin cancer, especially squamous cell carcinoma, coinciding with what is mentioned in the literature, which reports prolonged immunosuppression as the main cause^{2,4,8}. It is important to educate kidney transplant

patients, especially those with prolonged use of immunosuppressants, on the proper use of sun protection.

Among the dermatoses prior to kidney transplant, onychomycosis and HPV warts in all their varieties predominated, as reported by Fernández and Orozco¹⁴ on dermatoses in patients with chronic kidney failure. We stress the importance that all patients undergoing kidney transplant protocol be evaluated by the dermatology service to receive timely diagnosis and treatment in order to avoid subsequent complications, such as persistent onychomycosis, HPV warts and the development of squamous cell carcinoma, which shows a more aggressive behavior compared to the general population^{15,16}.

In published studies about dermatoses in kidney transplant patients, pre-transplant dermatoses have not been studied and should be considered for correlation with immunosuppression status.

Conclusions

Kidney transplant is the replacement therapy of choice in patients with advanced stage chronic kidney disease, as successful transplant is associated with longer survival and better quality of life. The mean age of patients with dermatosis was 37 years, ranging from 18 to 74 years. The group aged 18 to 30 years was predominant, because they are the patients of choice for kidney transplant and with less comorbidity. The sex with the highest number of dermatoses was male.

The most frequent cause of kidney disease in this study was undetermined and this may be due to the few biopsies performed in order to confirm the kidney diagnosis. In relation to comorbidity in kidney transplant patients, the highest percentage had no associated disease; in second place, the association with arterial hypertension was found, and in third place with type 2 diabetes *mellitus*. The predominance of kidney transplant recipients with no comorbidity identified at that time can be attributed to the fact that the group between 18 and 30 years of age predominated in our population. The most frequent type of donation in our study was from living donors, which can be attributed to the poor promotion and culture of organ donation. The immunosuppressive treatment most frequently used by this unit for kidney transplant patients is the mycophenolic acid, tacrolimus, and prednisone group. Previously, cyclosporine was used, but tacrolimus is now preferred due to its fewer side effects.

Infections were the most frequent dermatoses in kidney transplant patients. A total of 15 different types were diagnosed. The most common fungal infections

were onychomycosis and pityriasis versicolor, with an increase in the first 5 years after transplant. The second most frequent dermatosis was that caused by viral infections, the most common being HPV warts of all varieties, molluscum contagiosum, and herpes zoster.

Complete physical examination by a dermatologist prior to transplant is of utmost importance because there is a high frequency of onychomycosis and HPV warts in all their varieties that require treatment prior to transplantation. Otherwise, they could increase morbidity and mortality after transplant.

No study has reported the frequency of dermatoses caused by parasites. Our study concluded that the most frequent were demodicidosis and scabies.

Being multifactorial, skin cancer is more frequent in these patients. Therefore, it is mandatory to perform a complete interrogation and a thorough physical examination to look mainly for squamous cell carcinoma. This is the most common type of non-melanoma skin cancer in patients with immunosuppression, which makes it necessary to intentionally look for HPV warts that are refractory to treatment or that have existed for more than 5 years. Of the 153 patients evaluated, 8 had some type of skin cancer. Six of them presented squamous cell carcinoma; clinically, with topography and morphology similar to the general population. It affected zone H of the facial region and, morphology-wise, 5 of them were characterized by neoformations of nodular, keratotic aspect, and only one was ulcer-vegetative. As for the histological type, the biopsy review report indicated invasive variant in all cases, confirming a more aggressive variety in this type of patients. It should be noted that, of those 6 patients who presented with squamous cell carcinoma, 2 had a history of basal cell carcinoma, and only 1 patient had a history of flat, common HPV warts. Regarding the other 2 remaining patients, they were basal cell carcinomas without clinical and histological changes compared to the general population: clinically they affected the H-zone of the facial region and were characterized by a papular, pigmented neoformation with arboriform blood vessels on dermoscopy.

Actinic keratoses should be treated in a timely manner since their progression to squamous cell carcinoma is more rapid, aggressive and predisposes to greater mortality.

Sun protection and education of the patient with immunosuppression due to kidney transplant are essential to prevent non-melanoma cancer.

Among the inflammatory dermatoses, seborrheic dermatitis, which is associated with the patient's

immunosuppression, stands out. Clinically, they can be extensive areas and are typically refractory to the usual treatments.

There are few inflammatory dermatoses reported, and this may be due to the fact that patients receive immunosuppressive treatment, which is used for this type of dermatosis as well.

No association was found between dermatoses and the drug schedule, especially sebaceous hyperplasia due to cyclosporine, since only 2 patients of those studied were prescribed this drug.

No topographic or morphologic clinical changes were observed in the dermatoses compared to the general population, with the exception of the progress reported in the literature, according to which there is a tendency for squamous cell carcinoma to exhibit a greater clinical and histological aggressiveness.

Dermatologic examination should be considered a priority in all patients undergoing kidney transplant protocol, since dermatoses that could increase morbidity and mortality in these patients after transplant can be prevented or diagnosed and treated in a timely manner.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article

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