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Dermatological Findings Observed After Renal Transplantation in Patients

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ABSTRACT

Background: Renal transplant recipients tend to have a variety of skin diseases due to multiple immunosuppressive medications, accompanying co-morbidities and prolonged survival with the transplantation procedure. The aim of this cross-sectional study is to present dermatological findings and the contributing factors in renal transplant recipients.

Materials and Methods: Forty-one renal transplant recipients were examined by dermatologists between February and May 2021. The etiology of the chronic renal failure, the age at the time of the transplantation, time after transplantation, current medications, donor features, socio-demographic features of the patients, history of dialysis and accompanying co-morbidities were questioned.

Results: Average age of patients (27 male, 14 female) was 49.9±11.2 years. Average time after renal transplantation was 12.8±6.6 years. 87.8% of the patients were taking mycophenolate mofetil; 78% systemic steroids, 68.3% tacrolimus, 22% cyclosporin-A and 12.2% azathioprine. Skin signs due to immunosuppressive medications were more frequent in younger patients (p=0.031). Xerosis of the skin due to immunosuppressive medications was found in 41.5% and acneiform eruption in 34.1% of the patients. For skin infections, superficial fungal infections were the most frequent (73.2%), 56.1% of them being onychomycosis. Warts (22%) were the most frequent viral skin disease (31.7%). Viral and fungal skin infections were significantly more common in patients who are taking tacrolimus (p=0.024 and p=0.002, respectively). Fungal skin infections were more common in patients with prolonged and high-dose mycophenolate mofetil treatment (p=0.021 and p=0.005, respectively). Kaposi sarcoma was found in one of the patients and *in situ* squamous cell carcinoma was found in another patient. The most common oral lesion was gingival hyperplasia (29.3%).

Conclusion: Fungal and viral skin infections, skin cancers, acneiform eruptions, xerosis of the skin and gingival hyperplasia are commonly seen in renal transplant recipients. Therefore, proper dermatologic follow-up examinations are crucial.

Keywords: Renal transplantation, Xerosis, Acneiform eruption, Superficial fungal infections, Warts

Introduction

Renal transplantation is the most ideal and efficient treatment option of end stage renal failure and severe chronic renal diseases, besides improving the quality of patients' lives [1]. However, immunosuppressive treatment which is usually necessary for

lifetime to prevent the rejection of the transplanted kidney makes the patients prone to skin diseases like infections and non-melanoma skin cancers [2,3,4]. In addition, several accompanying comorbidities and prolonged life expectancy after transplantation increase this trend [5]. For these reasons, it is very important for the renal transplant recipients to undergo patients who have had



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kidney transplantation have regular follow-up for with dermatologic examinations. This is necessary not only to prevent the impact of possible dermatological diseases on the patients' quality of life but also to properly manage the complications that may occur.

The aim of this cross-sectional study is to review the skin diseases in renal transplant recipients and possible contributing factors that may affect them such as immunosuppressive medications, time after transplantation and donor characteristics.

Materials and Methods

We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Medeniyet Training and Research Hospital Local Ethics Committee (date: 13.01.2021, approval number: 0003). Forty-one patients who were being followed-up after kidney transplantation at the Nephrology Department of the Medeniyet Training and Research Hospital of the Istanbul University, and agreed to participate in the study were examined by dermatologists of the same hospital between February 1st and May 30th, 2021. Patients were questioned about their socio-demographic characteristics, age at the time of renal transplantation, disease that caused renal failure, donor characteristics, the type and duration of the immunosuppressive treatment, accompanying comorbidities and the history of dialysis. The patients provided written consent stating that they agreed to participate in the study.

Statistical Analysis

The data obtained in the study were analysed with the Statistical Package for the Social Sciences IBM 25.0 package data program. Descriptive statistics (mean-standard deviation) and frequency distributions are presented. Independent group comparisons test statistics on continuous measurements were calculated by Mann-Whitney U test and binary group comparisons were calculated by chi-square test. The confidence level is set at 95%. A p value below 0.05 was considered significant.

Results

Socio-demographic Characteristics, Transplantation History and Accompanying Diseases of the Patients

A total of 41 patients participated in our study, 14 of whom were women and 27 of whom were men. The mean age of the patients was 49.9 ± 11.2 years (21-70). The socio-demographic characteristics of the patients, the diseases that necessitated the transplantation, the time after transplantation, the characteristics of the donor and accompanying comorbidities are summarized in Table 1.

Of all the patients, 90.2% were treated with either peritoneal dialysis or haemodialysis before transplantation. Average duration of dialysis was 1.9 ± 0.3 years. Two of the patients (4.9%) had

admitted to the dermatology outpatient clinic while on dialysis. A patient was diagnosed with dermatofibroma, and the other one was treated for tinea pedis and corporis. Eight patients (19.5%) admitted to the dermatology department by themselves due to skin problems after transplantation. These patients were diagnosed with seborrheic keratosis, stasis dermatitis, zona zoster, irritant contact dermatitis, dermal nevus, macular drug eruption due to antidiabetic medications, genital warts and pityriasis versicolor. Thirty-four (82.9%) of the patients had accompanying comorbidities, hypertension being the most frequent one (53.6%), followed by diabetes mellitus (26.8%) and hypercholesterolemia (7.3%). Five patients (12.2%) had systemic cancers. Two had prostate cancer, 2 had papillary thyroid cancer and one had colon carcinoma.

The Immunosuppressive Treatment and Skin Signs Associated with These Medications

The medications, doses and duration of the treatment of patients after renal transplantation are summarized in Table 2. For systemic treatment, 87.8% of patients were taking mycophenolate mofetil, 78% corticosteroids, 68.3% tacrolimus, 22% cyclosporin-A and 12.2% azathioprine.

Skin findings due to immunosuppressive drugs were observed in 85.4% of patients. These findings were more frequent in young patients. The mean age of those with skin findings was $48 \text{ years} \pm 11$ years, while those without skin findings were $59 \text{ years} \pm 8$ years ($p=0.031$).

Most commonly, 41.5% of patients had xerotic body skin followed by acneiform eruption in 34.1%, seborrhoea on the face in 31.7%, sebaceous gland hyperplasia in 24.4%, gingival hyperplasia in 22%, flushing in 17.1%, facial telangiectasia in 12.2%, demodicosis in 12.2%, striae in 9.8%, moon face in 7.3%, purpura in 7.3%, dorsocervical fat accumulation in 2.4% of the patients (Figure 1).

Skin Infections

Superficial fungal infections were found in 73.2%, viral infections in 31.7%, parasitic (all cases demodicosis) in 12.1% and bacterial skin infections in 9.8% of the patients.

Fungal infections were more common as the time after transplantation was prolonged. The mean time after transplantation was 14 ± 7 years in patients with fungal infections, while it was 9 ± 4 years who did not have fungal infections ($p=0.036$). In addition, fungal infections were common in patients who were taking tacrolimus and mycophenolate mofetil for a longer period. Average duration of tacrolimus therapy was 98 ± 99 months in patients with fungal infections, while it was 86 ± 51 months in patients without fungal infection ($p=0.002$). For mycophenolate mofetil, average duration of therapy was 173 ± 85 months in patients with fungal infections vs 72 ± 77 months ($p=0.021$). Fungal infections

were also more frequent in patients who were on higher doses of mycophenolate mofetil (1135±487 mg/day vs 456±401 mg/day, p=0.005). For the distribution of fungal infections, onychomycosis of the feet was found in 48.8% of patients, onychomycosis of hands in 7.3% of, tinea pedis in 43.9%, pityriasis versicolor in 24.4%, tinea cruris in 2.4% and candida infections in 2.4% (Figure 2A, 2B). One of the patients had a history of deep fungal infection in the leg which had healed with scar formation.

Viral skin infections were more common in patients with longer duration of accompanying comorbidities (18±10 years vs 4±7 years,

p=0.002). Of all patients on tacrolimus treatment, 57.1% had viral skin infections, while 42.9% did not (p=0.024). However, neither duration nor dose of tacrolimus were correlated with viral infections (p=0.822; p=0.219, respectively). Warts were the most common viral skin infection (22%) (Figure 2C). The most common location were feet (12.2%), followed by hands (9.8%), and other parts such as body and face (7.3%). Zona zoster was found on the leg of a patient. 12.2% of the patients had history of zona zoster with one of them recalcitrant postherpetic neuralgia. Active herpes simplex infection was found in 14.6% of patients (lips 9.8%, nose 4.9% and face 4.9%,

Table 1. The socio-demographic characteristics, primary diseases, and information about renal transplantation of patients

		Number	%
Gender	Female	14	34.1
	Male	27	65.9
Marital status	Married	25	61.0
	Single	16	39.0
Age	49.9±11.2 years		
Education level	Middle school and lower	18	43.9
	High school and higher	23	56.1
Smoking status	Smoker	8	19.5
	Non-smoker	21	51.2
	Ex-smoker	12	29.3
Smoking pack year	9.2±11.5 years		
Alcohol consumption	Regular	1	2.4
	None	29	70.7
	Social	11	26.8
Are parents related	No	33	80.5
	Yes	8	19.5
	Parents are sibling children	2	4.9
	Parents are cousin children	6	14.7
Duration after transplantation	12.8±6.6 years		
Transplantation age	38.4±10.9 years		
Etiology of primer renal failure	Immunoglobulin A nephropathy	2	4.9
	Hypertension	7	17.1
	Glomerulonephritis	4	9.8
	Alport syndrome	2	4.9
	Diabetes mellitus	5	12.2
	Infection	11	26.8
	Polycystic kidney disease	5	12.2
	Renal atrophy	2	4.9
	Vesicoureteral reflux	2	4.9
	Unknown	1	2.3
Donor characteristics	Stranger	23	56.1
	Consanguineous	18	43.9
	Brain death	17	41.5
	Live donor	24	58.5

respectively). Of the patients, 43.9% had a history of recurrent herpes simplex infection (Table 3). Molluscum contagiosum was found on the arms of a patient (Figure 2D).

Folliculitis (7.3%) was the most commonly bacterial skin disease and paronychia of both toes was found in a patient.

Malignant and Premalignant Lesions

Malignant and premalignant lesions were found in 26% of patients. Actinic keratosis and lentigo were seen in two patients and dysplastic nevus were seen in a patient. A patient was diagnosed with Kaposi’s sarcoma which was located on the hand, foot and abdomen. *In situ* squamous cell carcinoma was found in one patient which was located on the back (Figure 3A). Two of the patients had a history of squamous cell carcinoma on the forehead and scalp which had been diagnosed previously.

Nevi

Various types of nevi were found in 17.1% of patients. Four patients had dermal and compound nevi, two patients had congenital nevi and a patient had nevus sebaceous (Figure 3B). Nevi were common in elderly patients; average of patients with nevi was 59±13 years versus 48±10 years in patients who did not have nevi (p=0.011).

Oral Lesions

Various oral lesions were detected in 53.7% of the patients. Oral lesions were more common in patients who were taking tacrolimus

than those who did not (57.14% and 42.86%, respectively, p=0.042). Gingival hyperplasia was the most common lesion (29.3%), followed



Figure 1. Skin findings of the patients due to immunosuppressive treatments. A) Acneiform eruptions on body. B) Seborrhea, sebaceous gland hyperplasia, facial telangiectasia on the face. C) Flushing and facial telangiectasia on the face. D) Striae on the abdominal area

Table 2. Drugs usage due to kidney transplantation		
Drugs		Number (%)
Systemic corticosteroid	None	9 (22)
	Yes	32 (78)
	Duration (months)	128.5±98.8
	Dose (mg/day)	3.9±2.6
Tacrolimus	None	13 (31.75)
	Yes	28 (68.25)
	Duration (months)	95.1±87.9
	Dose (mg/day)	1.9±1.6
Mycophenolate mofetil	None	5 (12.25)
	Yes	36 (87.75)
	Duration (months)	145.8±93.8
	Dose (mg/day)	948.5±553.1
Azathioprine	None	36 (87.8)
	Yes	5 (12.2)
	Duration (months)	12.3±38.1
	Dose (mg/day)	8.54±24.1
Cyclosporin-A	None	32 (78)
	Yes	9 (22)
	Duration (months)	47.7±96.8
	Dose (mg/day)	28.1±57.9

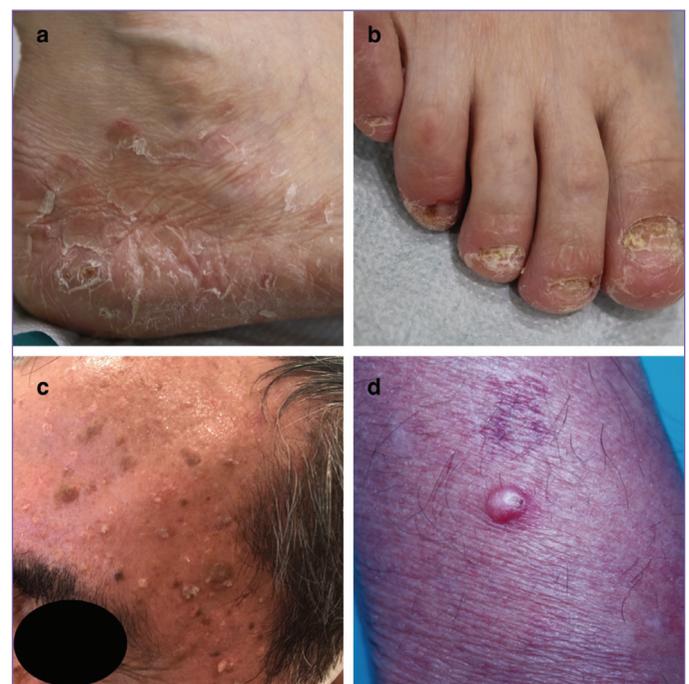


Figure 2. Skin infections of the patients. A) Tinea pedis. B) Onychomycosis on feet nails. C) Warts and also seborrheic keratosis on the face. D) Molluscum contagiosum on the arm

by atrophic glossitis (19.5%), hairy tongue (14.6%) and actinic cheilitis (4.9%) (Figure 3C).

Other Skin Lesions

Other skin lesions found in patients are summarized in Table 4. These lesions were more frequent in patients who were older at the time of transplantation (39±11 years) than the younger ones (32±4 years) (p=0.038). They were also more frequent in elderly patients (60±9 years) than younger patients (48±11 years) (p=0.026). In addition, ephelides, contact dermatitis, vitiligo, nail discoloration, dermatofibroma, pincer nail, half and half nail, rosacea, milium cyst, splinter haemorrhage, lipoma, ganglion cyst and hypertrophy of the shunt area were detected in different patients (Figure 3D).

Discussion

Our study has shown that patients with renal transplantation may have skin lesions and diseases of a varying spectrum, due to both the effects of the immunosuppressive medications and accompanying comorbidities. Dermatological side effects of the medications were more frequent in younger patients among which xerotic skin and acneiform eruptions were the most common ones.

The most common infections were superficial fungal infections, followed by viral infections. While tacrolimus and mycophenolate mofetil increased the tendency to fungal infections, tacrolimus increased the tendency to viral infections, too. Tendency to fungal infections increases as the period after transplantation gets longer and tendency to viral infections increases with the duration of accompanying comorbidities. Renal transplant recipients are also prone to skin malignancies.

It is known that skin lesions are more common in renal transplant recipients compared to normal population [2,6,7]. Among these, skin infections especially fungal and viral infections, non-melanoma skin cancers, gingival hyperplasia, alopecia and hirsutism are reported to be most common ones [7,8].

Fungal skin infections are the most common skin infections in renal transplant recipients with reported rates of 18-68% [2,9,10,11]. Fungal infections were also the most common infection in our study with a slightly higher rate (73.2%). Tendency to fungal infections increased as the time after transplantation get prolonged. Most common fungal infection was onychomycosis (56.1%) in our study. Onychomycosis was reported at a similar rate by Sandoval et al. [12] (58%), while Kartal et al. [13] reported only 5.3%. Ghaninejad et al. [11] reported pityriasis versicolor in 35% of the patients as the most common fungal infection. Pityriasis versicolor was slightly less frequent in our study (24.4%). However, in the study by Kartal

		Number (%)
History of herpes simplex	None	23 (56.1)
	Yes	18 (43.9)
Which part of the body	Lips	17 (41.5)
	Nose	1 (2.4)
Number of repetitions in a year		3.1±2.6
Recovery time	Days	7.25±5.01
Duration of herpes simplex repetition	Years	16.9±7.1

Findings	Number (%)
Seborrheic keratosis	11 (26.8)
Hyperpigmentation	10 (24.2)
Acrochordon	9 (22)
Ecchymosis	4 (9.8)
Androgenic alopecia	5 (12.2)
Pruritus	4 (9.8)
Onychodystrophy	4 (9.8)
Senile angioma	4 (9.8)
Seborrheic dermatitis	3 (7.3)
Telogen effluvium	3 (7.3)
Onycholysis	2 (4.9)
Unguis incarnatus	2 (4.9)
Dermoid cyst	2 (4.9)



Figure 3. Different skin findings of the patients. A) *In situ* squamous cell carcinoma on the back of a patient. B) Nevus sebaceous on ear. C) Gingival hyperplasia. D) Hypertrophy of the shunt area on kidney seen on skin

et al. [13], this rate was 2.1%. Since superficial fungal infections are very common in society, it should be considered natural to see them frequently in renal transplantation patients undergoing immunosuppressive treatment as well.

Viral skin infections rates between 13-29.3% were reported among renal transplant recipients [2,10]. Warts were the most common viral infection in all studies. While the incidence of warts was reported between 15-32.3% in cross-sectional and retrospective studies, this rate increases to 92% in the follow-up cohort [5,7,13,14,15]. Although viral infection rates were slightly more frequent in our study (31.7%), warts (22%) were the most common one which is similar to the previous reports. Ghaninejad et al. [11] reported herpes infection in 34% of their cohort. Dymock [16] reported herpes simplex infection in 39% of patients in a retrospective analysis. Moloney et al. [7] reported recurrent herpes infection in 4.6% of the patients. Active herpes infection was found in 4.6% of patients in our study, however, 43.9% of patients had a history of recurrent herpes infection. The relatively less rate of active herpes infection in our study may be attributed to the cross-sectional nature. However, the rate of recurrent herpes infection history was similarly high. The higher rates of both warts and herpes infections are associated with immunosuppressive treatments.

Rate of bacterial skin infections were not frequent in our study (9.8%), but acneiform skin lesions were considered among bacterial infections in some studies. The rate of acneiform eruptions was 34.1% in our study. This rate has been reported between 17-60% in previous studies [2,11]. It is quite natural to find acneiform lesions which are an expected side effect of systemic corticosteroid treatment in renal transplant recipients who depend on low dose systemic corticosteroids nearly lifelong.

Malignant and premalignant skin lesions are more common in renal transplant recipients. Skin cancer rates were reported to be between 4.7-35% in the published studies [7,12,15]. Malignant and premalignant lesions were found in 26% of patients with a skin cancer rate of 4.8% in our study. However, 9.8% of our patients had a history of previously diagnosed skin cancer after transplantation. Renal transplantation patients should be monitored regularly in terms of skin cancers that are found more commonly than society. In addition to these findings, xerotic skin (41.5%), seborrhoea and sebaceous gland hyperplasia (31.7%; 24.4%, respectively) and gingival hyperplasia (22%) were also noted. Rate of xerotic skin was slightly lower in previous studies (2.1-33%) in comparison to our study [2,7,10,13]. This difference can be explained by the fact that our patients are prone to xerosis due to slightly older age compared to previous studies. Moloney et al. [7] reported sebaceous gland hyperplasia in 17.3% of patients. This rate, which was 24.4% in our study, was more commonly found in patients who had

been taking cyclosporin-A for a long time. Gingival hyperplasia is noted as the most common oral lesion in many studies. However, Kartal et al. [13] and Engin et al. [2] have not observed gingival gland hyperplasia at all. The incidence of gingival hyperplasia was reported between 1.9-44% in previous studies, compared to 22% in our study [11,16,17,18]. Gingival hyperplasia has also been found more frequently in patients taking cyclosporin-A.

Study Limitations

The limitation of our study is that it was carried out with relatively few patients due to the circumstances of Coronavirus disease-2019 pandemic. More studies are needed with a greater number of patients who are followed up for a longer period.

Conclusion

Renal transplant recipients are particularly prone to fungal skin infections such as onychomycosis, viral skin infections such as warts and life-threatening skin cancers. In addition, acneiform eruptions, xerotic skin, sebaceous gland hyperplasia and gingival hyperplasia are also common due to the immunosuppressive medications. Therefore, it is very important to carry out regular dermatological follow-up for renal transplant recipients to prevent possible comorbidities and to enable proper and timely interventions.

Ethics

Ethics Committee Approval: We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the Istanbul University Medeniyet Training and Research Hospital Local Ethics Committee (date: 13.01.2021, approval number: 0003).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.K., H.A., Concept: M.A.K., H.A., Design: M.A.K., S.A.E., N.A., Data Collection or Processing: M.A.K., S.A.E., H.A., Analysis or Interpretation: M.A.K., S.A.E., Literature Search: M.A.K., H.A., Writing: M.A.K., N.A.

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