

Epidemiology of Skin Diseases in Renal Transplant Recipients in a Tertiary Hospital

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Abstract

Introduction: There is no published epidemiological data on skin diseases in kidney transplant recipients in this tropical country, which has multi-ethnic groups with the Chinese as the predominant ethnic group. **Materials and Methods:** Skin diseases of 143 renal transplant recipients were studied in a skin clinic of a tertiary institution during annual surveillance visits from June 2006 to March 2009. **Results:** Our study showed that except the common drug specific skin manifestations, sebaceous hyperplasia (56.6%), seborrheic keratosis (60.8%), melanocytic naevi (76.9%), skin tags (37.1%) and viral (29.4%) and fungal (20.3%) infections were the most prevalent skin diseases among renal transplant recipients living in Singapore. The prevalence of pre-malignant and malignant tumours was very low (11.2% actinic keratosis, 1.4% Bowen's disease, 1.4% squamous cell carcinoma, 0.7% basal cell carcinoma, 0.7% keratoacanthoma). Male predominance was seen in sebaceous hyperplasia (72.4% vs 32.1%), actinic keratosis (17.2% vs 1.8%), viral (36.8% vs 19.6%) and fungal (27.6% vs 8.9%) infections. Our study also showed increased prevalence of sebaceous hyperplasia with increased age but its prevalence was significantly higher than that reported in the age matched general population. The prevalence of seborrheic keratosis, actinic keratosis and viral infection correlated positively with post-transplant duration. **Conclusions:** Our study provides epidemiological data for the prevalence of skin diseases in renal transplant recipients. It emphasises the importance of dermatologic follow-up for renal transplant patients in order to obtain a diagnosis and manage treatable skin diseases.

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Keywords: Actinic keratosis, Sebaceous hyperplasia, Seborrheic keratosis

Introduction

Various types of skin lesions are more common in renal transplant recipients compared to the general population, mainly attributable to post-transplant immunosuppression. The well-documented drug-specific skin manifestations include cyclosporine-related hypertrichosis, gingival hypertrophy, steroid-induced acneiform eruption and striae. Apart from these, the skin lesions in renal transplant recipients differ markedly by gender, age, ethnic group, skin type and geographical location, as reported by various groups.¹⁻⁴ There has been no concise report of epidemiological data on skin lesions in renal transplant recipients in the Chinese population so far. Only a few studies focusing on malignancies and one study focusing on viral infection were done in renal transplant recipients in the Chinese population.⁵⁻⁸ Singapore is a tropical country

with a multi-ethnic group distribution, the predominant ethnic group of which is Chinese. The aim of our study was to analyse the spectrum of skin lesions among renal transplant recipients living in Singapore.

Materials and Methods

One hundred and forty-three renal transplant recipients were examined for the presence of skin lesions in the skin clinic during annual surveillance visits from June 2006 to March 2009. This was a retrospective study. Clinical, biological, biochemical and demographic data were retrieved from medical records of renal transplant recipients who underwent annual skin surveillance. Skin cancer was diagnosed based on histological findings from a skin biopsy.

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Fungal infection was diagnosed based on both clinical findings and fungal microscopy of skin scrapings. Data were processed using Microsoft excel XL, SPSS statistics software version 17.0 and Graphpad Prism. Numerical variables were described using mean \pm standard deviation (SD). Nominal variables were described using frequencies and percentages. The correlation of two nominal variables was analysed using chi-square. Statistical significance was taken at the $P < 0.05$ level.

Results

Of the 143 renal transplant recipients living in Singapore, 87 (60.8%) were male and 56 (39.2%) were female. Ages ranged between 20 to 71 years with mean of 50 years. Ethnic distribution was 119 Chinese (83.2%), 14 Malay (9.8%) and 9 Indian (6.3%) and 1 other (0.7%). The duration after transplantation ranged between 6 months to 266 months with mean of 69 months. Patients had received kidneys from either living or deceased donors including 26 living related donor (LRD, 18.2%), 8 living unrelated donor (LURD, 5.6%) and 107 deceased donor (DD, 74.8%). Spouse donors were categorised as biologically LURD (Table 1).

All patients were kept on immunosuppressants with various combinations of prednisolone, cyclosporine, tacrolimus, azathioprine, and mycophenolic acid. Newer types of immunosuppressants such as sirolimus, or

Table 1. Demographic Details of 143 Renal Transplant Patients (Cont'd)

		Frequency	Percent
Skin conditions	Sebaceous hyperplasia	81	56.6
	Seborrheic keratosis	87	60.8
	Melanocytic naevi	110	76.9
	Dermatofibroma	10	7.0
	Lipoma	3	2.1
	Sebaceous adenoma	1	0.7
	Steatocystoma	1	0.7
	Nodular hidradenoma	1	0.7
	Cherry angioma	27	18.9
	Skin tag	53	37.1
	Keloid	4	2.8
	Actinic keratosis	16	11.2
	Bowen's disease	2	1.4
	SCC	2	1.4
	BCC	1	0.7
	Keratoacanthoma	1	0.7
	Viral infection	42	29.4
Fungal infection	29	20.3	
Bacterial infection	5	3.5	
Drug-specific	74	51.7	

DD: deceased donor; LRD: living related donor; LURD: living unrelated donor; SCC: squamous cell carcinoma; BCC: basal cell carcinoma

Table 1. Demographic Details of 143 Renal Transplant Patients

		Frequency	Percent
Total		143	
Gender	Male	87	60.8
	Female	56	39.2
Age (years)	20 - 40	17	11.9
	41 - 50	46	32.2
	51 - 60	59	41.3
	61 - 71	21	14.7
Race	Chinese	119	83.2
	Indian	9	6.3
	Malay	14	9.8
	Other	1	0.7
Transplant type	DD	107	74.8
	LRD	26	18.2
	LURD	8	5.6
	Unknown	2	1.4
Post-transplant duration (months)	6 - 24	22	15.4
	25 - 60	59	41.3
	61 - 120	44	30.8
	120 - 266	18	12.6

everolimus were introduced to a small percentage of patients. The most common regimens are the combination of prednisolone, cyclosporine with mycophenolic acid; or prednisolone, cyclosporine with azathioprine; or prednisolone, tacrolimus with mycophenolic acid; and prednisolone, tacrolimus with azathioprine. The regime components and doses were modified over time.

The skin lesions were divided into several groups: benign tumour, pre-malignant tumour, malignant tumour, infection, drug specific skin manifestation and other skin lesions such as sebaceous hyperplasia. Benign skin tumour group includes seborrheic keratosis, melanocytic naevi, dermatofibroma, lipoma, and cherry angiomas. Melanocytic naevi, seborrheic keratosis and skin tag had high prevalence in our renal transplant recipients at numbers of 110 (76.9%), 87 (60.8%) and 53 (37.1%), respectively.

In the premalignant tumour group, a total of 16 patients (11.2%) had actinic keratosis, 2 patients (1.4%) had Bowen's disease and 1 patient (0.7%) had keratoacanthoma. However, among a total of 143 patients, there were only 3 (2.1%) histologically confirmed non-melanoma skin cell (NMSC) including 2 (1.4%) squamous cell carcinoma (SCC) and 1

(0.7%) basal cell carcinoma (BCC). There was 1 patient who presented with porocarcinoma, Bowen’s disease, SCC and keratoacanthoma. There was no Kaposi’s sarcoma or melanoma in our follow-up patients.

Infections include viral, fungal and bacterial infection. Among a total of 42 (29.4%) patients with viral infection, nearly all (41) had viral warts and only 1 had herpes zoster. Among a total of 29 (20.3%) patients with fungal infection, most (25) were pityriasis versicolor, 1 candida albicans, 1 tinea pedis, 1 tinea corporis and 1 onychomycosis. There were only 5 (3.5%) patients with bacterial infection. The incidence of bacterial infection was extremely low compared to the Indian and Turkish studies.^{1,2}

Drug-specific skin manifestations including cyclosporine related hypertrichosis, gingival hypertrophy, steroid induced acneiform eruption and striae etc are very well documented and we shall not elaborate here.⁹The prevalence of sebaceous hyperplasia was 56.6% among the renal transplant recipients.

In the general population, the gender difference in prevalence of sebaceous hyperplasia is unknown. However, it is interesting to find that among our renal transplant recipients, there were more males than females having sebaceous hyperplasia (72.4% vs 32.1%). Our study also showed that more male recipients had actinic keratosis than female (17.2% vs 1.8%), the difference being much exaggerated compared to the gender differences in the general population.¹⁰ Similarly, a higher prevalence of viral infection in male than female recipients (38.8% vs 19.6%) and fungal infection (27.6% vs 8.9%) was found in our study (Fig. 1).

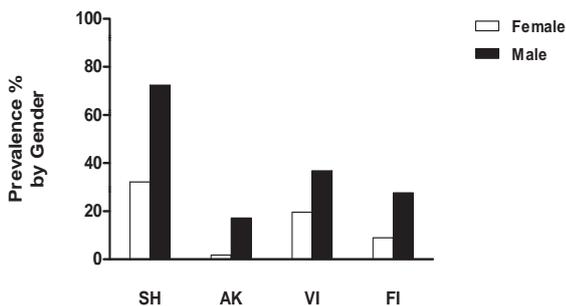


Fig. 1. The correlation of prevalence of skin conditions with gender. Among all the skin conditions, only SH, AK, VI and FI correlated with gender with higher prevalence in males. The correlations were statistically significant with *P* value < 0.05. The other types of skin conditions were not associated with gender. SH: sebaceous hyperplasia; AK: actinic keratosis; VI: viral infection; FI: fungal infection

Sebaceous hyperplasia begins to appear in middle age (usually fifth or sixth decade) and continues to appear in later life in the general population. Its prevalence in the general population is around 1%. Likewise, seborrheic keratosis is the most common benign tumour in older individuals and it appears to increase with age. In our renal transplant recipients, following the pattern in general population, there was more sebaceous hyperplasia in older patients (23.5% vs 56.5% vs 61.0% vs 71.4% for patients with ages of 20 to 40, 41 to 50, 51 to 60 and 61 to 71 respectively). Similarly there was also more seborrheic keratosis in older patients (23.5% vs 56.5% vs 69.5% vs 76.2% for patients with ages of 20 to 40, 41 to 50, 51 to 60 and 61 to 71 respectively) (Fig. 2).

There was correlation between post transplant follow-up duration and seborrheic keratosis, actinic keratosis, viral infection with much higher prevalence of these skin

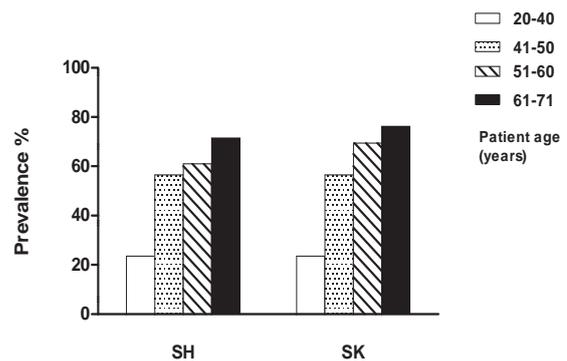


Fig. 2. The correlation of prevalence of skin conditions with age. Among all the skin conditions, only SH and SK were correlated with age with higher prevalence in older patients. The correlations were statistically significant with *P* value < 0.05. The other types of skin conditions were not associated with age. SH: sebaceous hyperplasia; SK: seborrheic keratosis

diseases in longer duration (Fig. 3). For example, there was increased prevalence of seborrheic keratosis especially for post transplant duration above 60 months (54.5% vs 47.5% vs 75.0% vs 76.5% for post transplant duration of 2 to 24, 25 to 60, 61 to 120 and 121 to 266 months). There was a dramatic increase in the prevalence of actinic keratosis for post transplant duration above 120 months (4.5% vs 8.5% vs 9.1% vs 35.3% for post transplant duration of 2 to 24, 25 to 60, 61 to 120 and 121 to 266 months). A gradual increase was observed for the prevalence of viral infection with the prolongation of post transplant duration (13.6% vs 25.4%

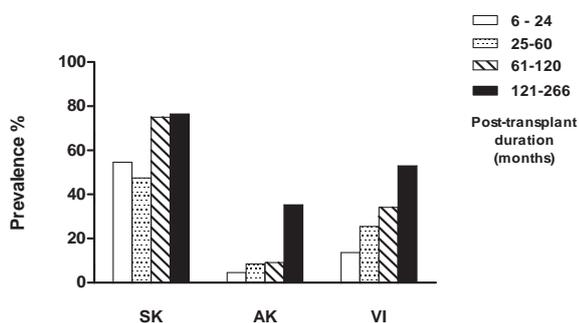


Fig. 3. The correlation of prevalence of skin conditions with post-transplant duration. Among all the skin conditions, only SK, AK and VI were correlated with post-transplant duration with higher prevalence in longer duration. The correlations were statistically significant with P value < 0.05 . The other types of skin conditions were not associated with age.

SK: seborrheic keratosis, AK: actinic keratosis, VI: viral infection

vs 34.1% vs 52.9% for post transplant duration of 2 to 24, 25 to 60, 61 to 120 and 121 to 266 months).

All the above correlations were statistically significant with $P < 0.05$. There was no correlation between gender, age or post-transplant duration with other types of skin diseases not mentioned above. It was also interesting to find that there was no correlation between ethnic groups or transplant types with any type of skin diseases.

Discussion

In our study, we described the epidemiology of skin diseases in renal transplant recipients in a tertiary institution in Singapore over 2 years and 9 months, determined the sub-classifications of diagnoses and established the statistical backdrop for future studies in skin disease.

Although ethnic group was assumed to have significant impact on the variance of skin lesions, we did not observe significant correlation between different Asian ethnic groups including Chinese, Malay and Indian with any types of skin diseases in post renal transplant recipients.^{11,12} This might be explained by the predominance of the Chinese population in our study and by the low risk of skin malignancies in Asians.¹³⁻¹⁵ Therefore, our data is very important for other Asian countries, particularly those with a majority of Chinese population.

It was well-studied that NMSC including SCC and BCC had increased incidence in renal transplant recipients.¹²⁻²⁰ Melanoma prevalence is also higher in renal transplant recipients.²¹ However, the overall prevalence of skin premalignancy and malignancy in our study was extremely low. The prevalence of skin premalignancy and malignancy

was much lower than in European and North American countries.^{11-13,16-20} This finding is consistent with other studies performed in renal transplant patients in China, India, Korea, Japan and Thailand.^{1,5-7,13-15} Although skin cancer is the seventh most common cancer in Singapore, the crude rate of skin cancer was 11.3 per 100,000 per year in Singapore according to the Singapore Cancer Registry Report Interim Report Trends in Cancer Incidence in Singapore 2003 to 2007.

Correlation between gender, age, and post transplant duration with various skin diseases were noticed in our study. All the listed correlations were statistically significant. However, whether or not they have significant clinical implications needs to be further investigated. For instance, it was very interesting to find that seborrheic keratosis had higher prevalence in our renal transplant recipients (60.8%) in comparison to general population, especially in longer post-transplant duration. Interestingly, while seborrheic keratosis is a benign epidermal tumour, it was reported in association with a number of other skin malignancies, most commonly BCC and infrequently melanoma.²² The other very common type of skin condition in our renal transplant recipients, occurring in 56.6% of patients, was sebaceous hyperplasia. Its prevalence in the general population is around 1% but is reported to be as high as 10% to 29.9% in patients receiving long-term immunosuppression with cyclosporin A.²³⁻²⁵

One limitation of this study was that it was an uncontrolled study. The prevalence in our study was compared with the statistical results from general population and the results from other study groups. However, prevalences of certain skin conditions such as seborrheic keratosis and actinic keratosis vary widely among different populations. Unfortunately there is also no local data or data from Chinese population available for direct comparison. Although we believe it is likely that the increased prevalences of sebaceous keratosis and actinic keratosis with post transplant period in our study had a direct correlation with the duration of post transplant period, we cannot exclude the contributory effect from age. The other limitation was that our patients did not have dermatological screening prior to transplantation or prior to starting immunosuppressants. Therefore, it was hard to conclude if the skin lesions existed before or developed after transplantation and hence the causal relationship with immunosuppression could not be established. Thirdly, this was a single-centre study. Lastly, correlation of nature of immunosuppression to the skin diseases could not be drawn as multiple drug regimes were used for our patients and multiple changes of the regimes and dosing occurred over time.

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