Original Article

Skin lesions in renal transplant recipients: A single center analysis

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ABSTRACT

Background: The chronic use of immunosuppressants in renal transplant recipients (RTRs) predisposes them to a variety of skin manifestations. Studies on skin lesions in RTRs from India have been limited. **Aim:** To study the prevalence and clinical spectrum of skin diseases in RTR in patients attending the Nephrology clinic of a tertiary care hospital in South India. **Methods:** Between October 2002 and June 2003, 365 RTRs were evaluated for skin lesions, including 280 examined after renal transplant (group A) and 85 examined once before and then monthly after transplant for a period of 6 months (group B). **Results:** A total of 1163 skin lesions were examined in 346 RTRs (94.7%) including lesions of aesthetic interest (LAI) [62.3%] followed by infections [27.3%]. All LAI were drug-related manifestations, making it the most common skin lesion, while fungal (58.7%) and viral (29.3%) infections constituted majority of lesions caused by infection. Lesions related to neoplasms were relatively uncommon (2.1%) and all lesions were benign. Miscellaneous lesions constituted 8.3% of skin lesions, which included vaccine-induced necrobiotic granulomas at the site of Hepatitis B vaccination and acquired perforating dermatoses. **Conclusion:** Skin lesions among RTRs from India consist predominantly of drug-related LAI and infections and are different from the West in view of the paucity of neoplastic lesions.

Key words: Renal transplant recipients, Skin lesions

INTRODUCTION

Renal transplantation is the standard form of therapy for patients with end-stage renal failure. The chronic use of immunosuppressants after transplantation with its various side effects, opportunistic infections and the increased risk of malignancies have the potential to affect the skin. Studies on skin manifestations in renal transplant patients have been predominantly from the West and there is paucity of data on skin lesions in renal transplant recipients from India.[1-3] The present study is an attempt to highlight the spectrum of dermatological lesions seen in renal transplant recipients in a tropical environment from a tertiary care hospital in South India

METHODS

All renal transplant recipients (RTRs) attending the renal transplant outpatient clinic between October 2002 and June 2003 were included in this study. Two groups of patients were included in the study. Group A: All RTRs who had already undergone a renal transplant and attending the renal transplant outpatient clinic.

Group B: Patients who were on maintenance dialysis and awaiting a renal transplant. These patients were seen just prior to renal transplant and then subsequently followed up monthly for a period of six months.

All patients seen in the renal transplant outpatient clinic were carefully examined for any skin lesions. A detailed proforma was filled for each patient, including demographic data, previous treatment, a detailed history of skin lesions and examination findings. Specific tests including skin scraping and

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KOH for suspected superficial fungal infections, Gram staining for suspected pyogenic infections, Ziehl Nielsen staining for suspected atypical and typical mycobacteria and skin smears for acid-fast bacilli for leprosy were done. Fungal, atypical and typical mycobacterial cultures were done in all patients who presented with chronic ulcerated lesions and nodules. Skin biopsies were done for all patients except those with pyogenic infections, superficial fungal infections, warts and lesions of aesthetic interest (LAI). Special staining with periodic-acid Schiff and Fontana-Masson stain for fungi, Ziehl-Nielsen stain for typical and atypical mycobacteria and Fite-Faraco stain for lepra bacilli were done whenever indicated.

After diagnosis, skin lesions were classified as follows:[4,5]

a) Lesions of aesthetic or functional interest (LAI), which consisted of all the drug-related manifestations
b) Skin infections
c) Skin neoplasms
d) Miscellaneous skin lesions

This study was approved by the Institutional Review Board of the hospital.

Statistical analysis

The percentage of various skin lesions occurring in RTR such as LAI, infections, neoplasms and miscellaneous lesions were calculated and the significance in difference, if any, was established using the Mann-Whitney U Test.

RESULTS

Between October 2002 and June 2003, we studied 365 consecutive RTRs, including 280 patients in Group A and 85 in Group B. Four patients (three in Group A and one in Group B) were seen following a second transplant. There were 294 men and 71 women with a mean age of 35.3 years (range: 12 – 65). The median interval duration between renal transplant and time of evaluation was 30 months (range: 0.5–240) for Group A. Eighty-one RTRs were seen beyond 5 years after renal transplant. A majority (80%) were on cyclosporine-based immunosuppressive therapy either alone or in combination with other agents, while 39 patients (10.7%) received either mycophenolate or rapamycin [Table 1].

Table 1: Baseline characteristics of renal transplant recipients

	Overall	Group A	Group B
Number of patients	365	280	85
Mean age (yrs)	35.3	36.1	32.8
	(12–65)	(12–65)	(13–59)
Sex			
Male	80.5%	80.7%	80%
	(294)	(226)	(68)
Female	19.5%	19.3%	20%
	(71)	(54)	(17)
Post-transplant duration (months)	30	30 (1–240)	<6 months
Immunosuppressive therapy			
CSA alone	1	1	0
CSA + Pred ± Aza ± MMF	292	209	83
CSA+ Rapa + Pred ± MMF	2	2	0
MMF + Pred ± Rapa ± Aza	11	10	1
Pred ± Aza ± Rapa ± Cyclo	59	58	1
Percentage of patients having skin lesions	346	261	85
	(94.7%)	(93.2%)	(100%)
Number of skin lesions present	1163	928	235

Group A: All RTRs who had already undergone a renal transplant and attending the renal transplant outpatient clinic. Group B: All patients who were seen initially prior to renal transplant and then followed up for six months. CSA, cyclosporine; MMF, mycophenolate; Pred, prednisolone; Cyclo, cyclophosphamide; Aza, azathioprine; Rapa, rapamycin

Skin lesions were seen in 346 patients (94.7%), with the majority being LAI (62.3%) followed by infections (27.3%), miscellaneous skin lesions (8.3%) and benign neoplasms (2.1%) [Table 2]. LAI were more frequent in the first two years following renal transplantation (61.4%) and gradually decreased with longer post-transplant duration (38.5%), while lesions caused by infections and benign neoplasms were more common in patients with longer post-transplant duration.

Lesions of aesthetic interest: Seven hundred twenty-five LAI were seen in 346 RTRs, including 573 lesions in Group A and 152 in Group B. Common lesions included moon facies (26.3%), acneiform eruptions (24.6%), hypertrichosis (10.3%), xerosis (7.5%), facial erythema (7.1%), atrophic skin (4.9%) and striae (3.9%). Other lesions seen included telangiectasia, gingival hyperplasia, epidermal cysts and facial edema. All LAI were drug-related manifestations, making it the most common skin lesion. Acneiform eruptions and xerosis were seen more in Group B, while other lesions were similar between both groups. In group B, 15% of LAI lesions were seen prior to transplant, 53% occurred within the first month, while less than 6% were seen more than 4 months after transplant.

Table 2: Incidence and time distribution of various skin lesions

	Lesions of aesthetic interest (n = 725)	Lesions caused by infection (n = 317)	Lesions caused by neoplasms (n = 24)	Miscellaneous lesions (n = 97)
Incidence of skin lesions				
Overall (n = 1163)	725 (62.3)	317 (27.3)	24 (2.1)	97 (8.3)
Group A (n = 928)	573 (61.7)	270 (29.1)	23 (2.5)	62 (6.7)
Group B (n = 235)	152 (64.7)	47 (20)	1 (0.4)	35 (14.9)
Time interval between transplant and skin lesions				
<6 months				
Group A (n = 204)	174 (85.3)	14 (6.9)	5 (2.4)	11 (5.4)
Group B (n = 235)	152 (64.7)	47 (20)	1 (0.4)	35 (14.9)
6–23 months* (n = 241)	178 (73.8)	51 (21.2)	1 (0.4)	11 (4.6)
24–59 months (n = 283)	147 (51.9)	107 (37.8)	4 (1.5)	25 (8.8)
>60 months (n = 200)	74 (37)	98 (49)	13 (6.5)	15 (7.5)

*None of the patients in Group B had a follow-up beyond six months, Figures in parentheses are in percentage

Lesions caused by infection: Skin lesions related to infection comprised 317 of 1163 (27.3%) skin lesions, with fungal infections being the most common (58.7%), followed by viral (29.3%) and bacterial infections (11.1%). Infestation with scabies was seen in three, of which one had crusted scabies. Viral infections were more common in the early transplant period (<6 months), while fungal infections were more common in those with longer transplant duration [Figure 1]. Deep fungal infections were relatively uncommon (1.5% of lesions related to infection). Tinea versicolor and candidiasis were seen with a shorter post-transplant duration, while dermatophyte infections were common in patients with longer post-transplant duration. Common viral lesions seen included were verruca vulgaris and verruca plana (62.4%), herpes simplex (27.9%), herpes/varicella zoster (7.5%) and molluscum contagiosum (2.2%). One patient had recurrent varicella. Herpes simplex infections were seen with shorter post-transplant duration (median: 12.2 months), while verruca vulgaris (median: 47 months), verruca plana (median: 79.1 months) and molluscum (median: 51 months) were seen with a longer follow-up. Bacterial infections consisted mainly of folliculitis (40%) and furunculosis (48.5%). One patient had granulomatous panniculitis consistent with tuberculosis diagnosed 36 months after second renal transplant, while two developed multibacillary lepromatous leprosy 12 and 13 years after renal transplantation.

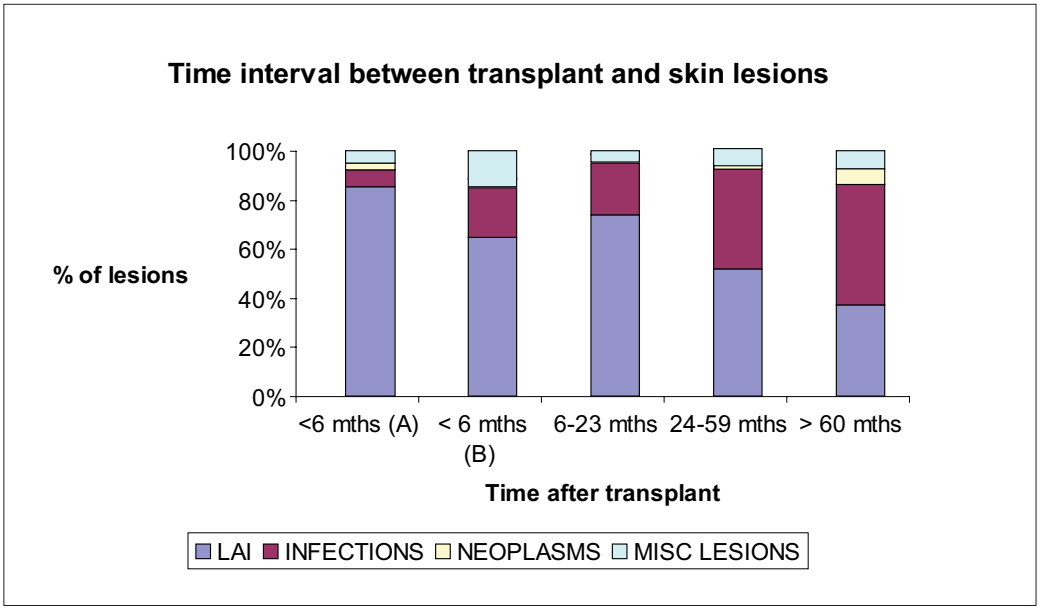

Figure 1: Distribution of skin lesions with respect to time post-transplant

Table 3: Cutaneous Benign Neoplasms Seen in Groups A and B

	Overall (n = 24)	Group A (n = 23)	Group B (n = 1)
Nevi	5	5	0
	(20.9)	(21.8)	
Acrochordon	7	7	0
	(29.2)	(30.4)	
Cherry angioma	3	3	
	(12.5)	(13.0)	0
Seborrheic keratosis	8	7	1
	(33.3)	(30.4)	(100)
Squamous papilloma	1	1	0
	(4.1)	(4.4)	

Figures in parentheses are in percentage

Lesions due to neoplasms: These were uncommon and seen in 24 patients (6.5%), comprising 2.1% of all skin lesions [Table 3]. All lesions were benign and included seborrheic keratosis (33.3%), acrochordon (29.2%), nevi (20.9%) and cherry angioma (12.5%). Nevi included were nevus spilus, Becker's nevus and dermal melanocytic nevus.

Miscellaneous skin lesions: Ninety-seven skin lesions were seen, which did not fit into the characteristic skin lesions described in RTR, and were classified as miscellaneous lesions. The most common lesion was hepatitis B vaccination scar (62.9%) that manifested as persistent nodules on the back at the site of intradermal hepatitis B vaccination and was seen in 61 of 365 patients (16.7%). Acquired perforating dermatosis was seen in 10 of 365 RTRs (2.7%) and in three patients, it was associated with a deteriorating renal function. Other lesions included fixed drug eruptions (FDE), keloids, melasma, vasculitis associated with antiphospholipid antibody syndrome (APS), macular amyloidosis, acute urticaria, geographic tongue, erythromelanosis, porokeratosis of Mibelli, psoriasis vulgaris, longitudinal melanonychia, leukonychia, half-and-half nails and diffuse alopecia.

DISCUSSION

Skin lesions are very commonly seen in RTR and this study has been conducted to highlight the spectrum of dermatological lesions seen in RTR in a tropical environment from a tertiary hospital from South India. We studied the prevalence of skin lesions in patients who had already undergone a renal transplant and prospectively studied the time profile of skin lesions in a group of patients who were followed up from before transplant till six-month post-transplant. The majority of RTRs (94.7%) had a skin lesion at the time of evaluation. LAI including drug-related manifestations comprised the major group of skin lesions in our study, similar to data from India and abroad [Table 4], although Vijaykumar *et al*,[3] showed a very low prevalence of drug-related manifestations. Neoplastic lesions were relatively uncommon in our study, which is different from the study reported by Strumia *et al*,[5] where a higher number of neoplastic lesions were reported (37%).

LAI were more common in the first six months following renal transplantation and were all drug-induced lesions. This may be related to the high dose of immunosuppressive drugs used in the initial period following renal transplantation where the risk of rejection is higher. Moon facies and acneiform eruptions were the most common LAI similar to observations in studies by Chugh *et al*[2] and Bencini *et al*,[6] related to the use of prednisolone and cyclosporine. The incidence of gingival hyperplasia was found to be similar (2.4% vs. 1.9%), although hypertrichosis was lower (9.9% vs. 41.1%) compared to data by Chugh *et al*,[2] even though a similar percentage of patients were on cyclosporine. Acneiform lesions were significantly higher in group B patients whose post-transplant duration was less than six months, as they are on higher doses of immunosuppressive medications during this period.

Table 4: Comparative data of skin lesions in renal transplant recipients

	RTR involvement	LAI	Infections	Neoplasms	Miscellaneous lesions
CMC study 2003					
(present study) (n = 365)	94.8	94.8	51.5	6.5	24.6
Chugh *et al*.[2] 1994 (n = 157)	88	84.7	52.2	0.6	-
Vijaykumar *et al*.[3] 1998 (n = 340)	51	19.5	35.6	0	-
Strumia *et al*.[5] 1992 (n = 53)	98	98	67.9	37.7	28
Bencini *et al*.[6] 1983 (n = 100)	95.2	55	74	12	3
Barba *et al*.[4] 1996 (n = 285)	-	82.3	30.9	4.3	-

All figures given in percentage

Fungal infections were the most common infective lesions similar to the other studies from India where between 60% and 75% of infections were caused by them. The overall prevalence of fungal infections in our study is similar to data from other centers in India[3] and the West[7,8] although it was lower than the prevalence reported from Chandigarh.[2] The prevalence of tinea versicolor (36.5%) is higher compared with other studies both from India[2] (13.3%) and the West[9] (18%). In a study from Turkey, Gulec *et al*,[7] in an analysis of 102 RTR showed a similar prevalence of tinea versicolor (36.3%). Among fungal infections, dermatophytosis accounted for only 10% of the total skin lesions, which is different from the study by Selvi *et al*,[1] where a prevalence of 42% was reported. Deep fungal infections were relatively rare in our study and one patient had a phaeomycotic cyst that recurred at the same site [Figure 2a]. There are a few case reports from India on the presence of phaeomycotic cysts in renal transplant recipients[10-12] caused by *Fonsecaea pedrosoi* and *Phialophora parasitica*. Chugh *et al*,[2] showed that two patients (1.3%) developed cutaneous nodules due to *Cryptococcus neoformans* along with meningitis. The true incidence of dematiaceous fungal infections among RTR is difficult to assess, as a majority are case reports.

Lesions caused by bacterial infections were seen in 11% patients similar to other studies from India (Chugh *et al*[2] – 8.9%) and the West (Barba *et al*[4] – 3.5%; Lugo-Janer *et al*[8] - 11%). The prevalence of cutaneous tuberculosis was very low in our study (0.3%) similar to data published earlier from our center.[13] There were only two cases of lepromatous leprosy. In an earlier study from our center, five patients developed leprosy at a median duration of three and a half years after transplantation.[14]

The incidence of viral infections (29%) is similar to data by Chugh *et al*[2] (21%), while studies from Italy (Bencini *et al*- 35%)[6] and United States (Koranda *et al* - 43%)[9] have shown a higher prevalence. In our study, viral warts were the predominant lesion (62%) and included both verruca vulgaris and verruca plana.

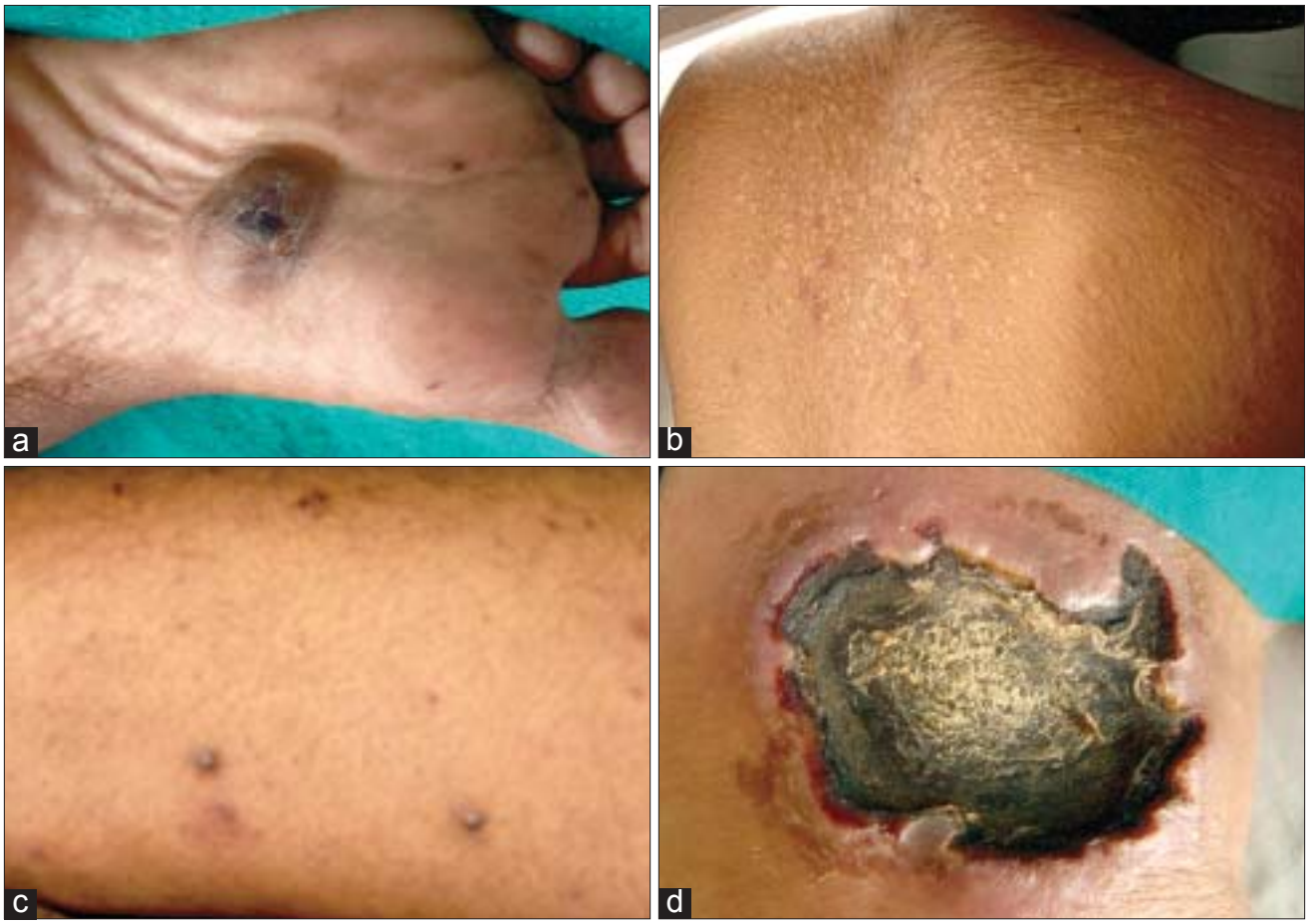

Figure 2: Rare Lesions in RTR. (a) Phaeomycotic cyst, (b) Persistent nodules at the site of intradermal hepatitis B vaccination with tinea versicolor, (c) Acquired perforating dermatosis, (d) Vasculitis associated with antiphospholipid antibody syndrom

Koranda *et al*,[9] showed a similar prevalence in their study on 200 RTRs (43%) although Chugh *et al*,[2] reported a prevalence of only 8.2%. Warts were seen more frequently in patients with a longer duration of functioning grafts (median: 47 months) similar to the reports by Barba *et al*,[4] Koranda *et al*[9] and Lugo-Janer *et al*.[8] Lesions caused by herpes simplex virus comprised 27% of viral lesions, which is similar to data from Koranda *et al*,[9] (35%), which included both genital herpes and herpes labialis. These were seen predominantly in patients with a shorter duration of functional grafts (median: 12.2 months). Herpes/ varicella zoster lesions was found to make up 7% of viral lesions similar to data from Chugh *et al* (10%).[2] There was a significant difference in the prevalence of lesions caused by viral infections between groups A and B. Herpes simplex virus infections were substantially higher in the first six months after transplant (Group B) compared to group A, which agrees with the data by Bencini *et al*,[6] while warts were more common in group A. Reactivation of latent viral infections caused by herpes group of viruses in the first six months may be related to the high degree of immunosuppression during that period. Herpes simplex infections may be associated with prolonged viral shedding, a decreased healing time and an increased viral dissemination in the immunocompromised host and a reduction in immunosuppressive therapy halted the dissemination and led to resolution of skin lesions.[15] Warts are found to be numerous and of greater proportion in the late recipients, as they are more related to the duration of immunosuppression rather than the degree of immunosuppression.[16,17]

Interesting skin lesions included persistent nodules at the sites of intradermal hepatitis B vaccination [Figure 2b]. This unusual reaction was reported earlier from our center in two RTRs. Histologically, these lesions proved to be necrobiotic granulomas.[18] The other common lesion seen in this group was acquired perforating dermatoses [Figure 2c], a majority of whom belonged to group A where the post-transplant duration was longer. A single case of acquired perforating dermatoses was reported by Chugh *et al*,[2] in their study on 157 RTRs (0.6%). The other interesting lesions included vasculitis of Antiphospholipid syndrome (APS) [Figure 2d], erythromelanosis follicularis of face and neck and macular amyloidosis.

In our study, all neoplasms described were benign. In a single western study involving 76 RTRs, the mean total number of benign melanocytic nevi was significantly higher in RTR compared to the normal population.[19] In Western studies, the incidence of cutaneous malignancies among RTR varied from 8% at 1 year to 44% at 15 years.[20-22] The cumulative effect of viral infections, prolonged immunosuppression and sunlight has been thought to predispose to the development of skin cancer in the transplant population. The incidence of skin cancer in the Indian study by Chugh *et al*[2] was only 0.6%, while in our study, there were no cutaneous malignancies. However, the duration of post-transplant follow-up for many patients in our study may not be sufficient to conclude that malignancies are fewer in this population. Boyle *et al*,[23] documented a link between exposure to UV radiation from sunlight and skin malignancies. The high melanin content of the Indian population may exert a protection against the development of cutaneous malignancies.[5] The melanin content and melanosomal dispersion pattern in people with phototypes V and VI is thought to be responsible for providing protection from the carcinogenic effects of UV radiation and hence a lower incidence of skin cancer.[24]

In conclusion, skin lesions are common in RTRs, with the major lesions being LAI followed by infections. Neoplastic lesions are very uncommon, with all being benign, while persistent nodules at the site of intradermal Hepatitis B vaccination were common.

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