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CUTANEOUS MANIFESTATIONS IN RENAL TRANSPLANT RECIPIENTS

Dermatology

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ABSTRACT

Background: The long term use of immunosuppressive therapy in renal transplant recipients (RTRs) predisposes them to various cutaneous manifestations. Studies on cutaneous lesions in RTRs from South India have been limited.

Aim: To study the prevalence and clinical spectrum of cutaneous diseases, and to correlate the duration of the immunosuppressive therapy that predisposed to various dermatosis in RTR patients.

Methods: In this study, 80 Renal Transplant Recipients attended the Dermatology and Nephrology clinic of a tertiary care hospital in South India on systemic immunosuppressive therapy were screened for cutaneous lesions.

Results: A total of 166 cutaneous lesions were examined in 80 RTRs of which fungal infections (87.5%) were most common followed by drug induced cutaneous lesions (66.2%), viral infections (28.7%) and bacterial infections (18.7%). Miscellaneous lesions constituted 6.2% of cutaneous lesions, which included exaggerated papular urticaria, lichen planus and keratosis pilaris.

Conclusion: Cutaneous lesions among RTRs from South India consist predominantly of fungal infections followed by drug induced cutaneous lesions and are different from the Western countries in view of the paucity of malignant lesions. Cutaneous manifestations were seen predominantly during the initial one year of post transplant period.

KEYWORDS

Renal transplant recipients, cutaneous lesions

INTRODUCTION

Renal transplantation is the treatment of choice for better quality of life in end stage renal disease patients[1]. Improvement in surgical techniques and advances in immunosuppressive therapy have led to a marked increase in the number of organ transplants worldwide and to long-term survival after transplantation. In renal transplant recipients, a state of generalized non-specific immunosuppression has been induced to prevent the rejection of graft by using various drugs (such as Corticosteroids, Cyclosporine, Tacrolimus, Azathioprine and Mycophenolate mofetil). The immunosuppression induced by drugs to prevent the graft rejection renders the renal transplant recipients more susceptible to bacterial, viral and fungal infections and predisposes to the various dermatosis, premalignant and malignant skin conditions which may cause significant morbidity and mortality. The consequence of immunosuppression differs markedly with geographical location, racial group and skin type[2].

The various cutaneous manifestations in renal transplant recipients has been evaluated by a limited number of studies in South India[3]. The present study is an attempt to highlight the spectrum of dermatological lesions and to correlate the duration of the immunosuppressive therapy that predisposed to various dermatosis in renal transplant recipients in a tropical environment.

MATERIALS AND METHODS

In this study, 80 renal transplant recipients on systemic immunosuppressive therapy attending the Department of Dermatology and Nephrology were screened. The detailed history of each patient was noted with reference to age and sex, symptomatology and duration of skin manifestations, family history of similar lesions, date of transplantation and immunosuppressive drug regimen and duration. The patients were examined thoroughly for all cutaneous manifestations. The duration of the cutaneous lesions, the size and extent of involvement were noted. The cutaneous lesions were classified as drug induced changes, fungal infections, viral infections, bacterial infections, neoplastic and miscellaneous lesions.

All the patients were subjected to routine hematologic investigations like complete haemogram, standard biochemical investigations like blood sugar, blood urea, serum creatinine, serum electrolytes, calcium and phosphate levels. Detailed urine examination was carried out in all of them. Screening for HIV was also done in all the renal transplant recipients. Mycological investigations in cases of fungal infections included microscopic examination of skin scales, mucosal scraping, pus and touch smear from skin biopsy were done after adding 10% Potassium hydroxide (KOH) solution. Nail scraping material was examined under light microscopy after adding 40% KOH in suspected cases of onchyomycosis. Gram stain and Ziehl Nielson stain were done in all suspected cases of cutaneous infection. Tzanck smear was done in vesiculobullous skin lesions. In willing patients, skin biopsy was done and the specimens were stained with Haemotoxylin and Eosin (H&E) and in required cases special stains like Periodic-acid Schiff (PAS) and Gomori's methenamine silver (GMS) were used to confirm the fungal infections.

Appropriate treatment was given for all the renal transplant patients presented with cutaneous lesions. Written informed consent was obtained from each patient and the study protocol was approved by the Institutional Ethical Committee.

OBSERVATIONS AND RESULTS

The total number of renal transplant recipients screened were 80, of whom 64 (80%) were males and 16 (20%) were females with the male to female ratio of 4:1. The age of these patients ranged from 16 years to 55 years with an average of 33.2 years (Table 1). The duration of immunosuppressive therapy following transplantation among the study group ranged from 2 months to 7 years. Various drug regimens has been used to induce immunosuppression to prevent graft rejection. The commonly used combination of drugs were Cyclosporine (CSA), Azathioprine (AZA) and Prednisolone (PDN) in 49 patients (61.25%), followed by Tacrolimus (TAC), Mycophenolate mofetil (MMF) and Prednisolone combination in 16 patients (20%). In patients who were on prolonged period of immunosuppression, the maintenance drug combination used were either Prednisolone with Azathioprine in 4 patients (5%) or Prednisolone with Mycophenolate mofetil in 3 patients (3.75%) as shown in below **Table 1.**

Table 1: BASELINE CHARACTERISTICS OF REAL TRANSPLANT RECIPIENTS

Number of Patients	80
Mean Age (years)	33.2, (16-55)
Sex, Male	80%, (64)
Female	20%, (16)
Post transplant duration (months)	7-12, (2-84)
Immunosuppressive regimen	CSA + AZA + PDN, 61.25% (49)
	TAC + MMF + PDN, 20% (16)
	CSA + MMF + PDN, 10% (08)
	AZA + PDN, 5% (04)

	MMF + PDN, 3.75% (03)
Percentage of patients having skin lesions	100 %

Number of skin lesions present	166

CSA - Cyclosporine AZA - Azathioprine PDN- Prednisolone TAC - Tacrolimus MMF- Mycophenolate mofetil

Table 2: THE PREVALENCE AND POST TRANSPLANT INTERVAL FOR CUTANEOUS MANIFESTATIONS IN RENAL TRANSPLANT RECIPIENTS

S.No	CUTANEOUS MANIFESTATION	POST TRANSPLANT INTERNAL FOR CUTANEOUS MANIFESTATION IN MONTHS					PREVALENCE PERCENTAGE
		0-6	7-12	13-24	25-60	>60	
1.	**Fungal infections M-61 F-09 T-70**	08	38	19	04	01	87.50
	a) Dermatophytosis M-26 F-00 T-26	-	12	12	02	-	37.14
	b) Pityriasis versicolor M-26 F-07 T-33	04	24	05	-	-	47.14
	c)Candidiasis M-04 F-02 T-06	04	02	-	-	-	8.5
	d) Phaeohypomycosis M-05 F-00 T-05	-	-	02	02	01	7.1
2.	**Drug Induced Changes M-42 F-11 T-53**	18	23	12	-	-	66.25
	a) Cushingoid facies M-19 F-04 T-23	07	11	05	00	-	43.3
	b) Acneiform eruptions M-10 F-03 T-13	10	03	00	00	-	24.5
	c) Striae M-04 F-01 T-05	01	04	00	00	-	9.4
	d) Hypertrichosis M-04 F-00 T-04	00	02	02	-	-	7.5
	e) Gum hyperplasia M-05 F-00 T-05	00	02	03	-	-	9.4
	f) Hirsutism M-00 F-03 T-03	00	01	02	-	-	5.6
3.	**Viral Infections M-19 F-04 T-23**	05	07	07	04	-	28.75
	a) Verrucae M-07 F-01 T-08	-	01	03	04	-	34.78
	b) Herpes Zoster M-08 F-01 T-09	-	05	04	-	-	39.13
	c) Herpes simplex M-01 F-02 T-03	03	-	-	-	-	13.04
	d) Varicella M-02 F-00 T-02	02	-	-	-	-	8.6
	e) Molluscum Contagiosum M-01 F-00 T-01	-	01	-	-	-	4.3
4.	**Bacterial Infections M-12 F-03 T-15**	06	05	04	-	-	18.75

M-Male F-Female T-Total

Cutaneous manifestations were seen predominantly during the initial one year of post transplant period. The most common manifestation was cutaneous infections, of which fungal infections were commonly seen and particularly during the 7 to 12 months of post transplant period. The viral infections were more commonly manifested during the 7 to 24 months of post transplant period. The bacterial infections were commonly seen during the initial 6 months of post transplantation. Cutaneous changes due to drugs were commonly observed during the first year of post transplantion, after which the incidence was gradually declined.

PREVALENCE OF SKIN MANIFESTATIONS IN RENAL TRANSPLANT RECIPIENTS (Table 2)

In this study, out of the 80 renal transplant recipients screened for cutaneous manifestations, 70 patients (87.5%) presented with fungal infection. This was followed by drug induced changes in 53 patients (66.25%), viral infections in 23 patients (28.75%) and bacterial infections in 15 patients (18.75%). Miscellaneous cutaneous lesions were encountered in 5 patients (6.25%). Out of 80 patients studied, fungal infections were seen in 70 patients giving an incidence of 87.5%. Of them 61 were male (88.4%) and 9 were females (11.5%). Their age ranged from 16 years to 55 years with an average of 24.5 years . Among the fungal infections pityriasis versicolor lesions were commonly encountered in 33 patients (47.14%), followed by dermatophytosis in 26 patients (37.14%), candidiasis in 6 patients (8.5%) and phaeohypomycosis in 5 patients (7.1%). Phaeohypomycosis was noted in 5 male patients (7.1%) and no females were affected and confirmed with histopathological examination of skin biopsy, and 10% KOH examination of touch smear (Figure 8b) and special staining with Periodic-acid Schiff (PAS) (Figure 1) and Gomori's methenamine silver (GMS) (Figure 2) showed moniliform fungal elements. Four patients were developed the lesion one year after the transplantation and one patient developed 60 months after the transplantation.

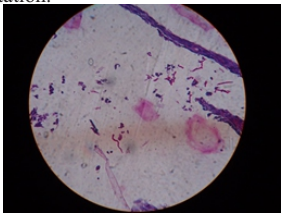

Figure 1: Periodic – Acid Schiff (PAS) stain shows Moniliform fungal elements suggestive of phaeohypomycosis

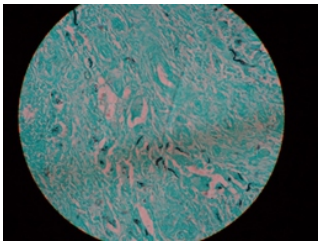

Figure 2: Gomori's Methenaminc silver (GMS) stain shows Moniliform fungal elements suggestive of phaeohypomycosis

The total number of patients observed to have viral infections were 23 (28.75%), of whom 19 were males (82.6%) and 4 were females (17.3%). The age of these patients ranged from 21 years to 55 years with an average of 36.5 years. Viral infections were more commonly noted between 7 months to 24 months of post transplant period. Herpes zoster was the commonest viral infection noted in this study group, as it was seen in 9 renal transplant patients (39.13%), out of 23 patients with viral infections. The lesions were seen in 8 (88.8%) males and 1 (11.1%) female. HPV infection was the second commonest type of viral infection in this study. Verruca vulgaris lesions were noted in 8 patients (34.78%), out of 23 patients with viral infections and the distribution of lesions were mainly confined to the extremities. Among the 8 patients with verruca, 7 patients were (87.5%) males and 1 female patient (12.5%). Infection with herpes simplex virus was noted in 3 (13.04%) patients, of whom 1 (33.3%) was male and 2 (66.6%) were females. All the three had herpes labialis. In this study herpes labialis was commonly seen during initial 6 months of post transplant period . Varicella infection was observed only in two male patients (8.6%), which were seen during the initial four months of transplantation. Molluscum contagiosum was observed in only one renal transplant patient (4.3%).

Bacterial infections were observed in 15 (18.75%) patients, of whom 12 (80%) were males and 3 (20%) were females. The age of these patients ranged from 26 years to 43 years with an average of 34.6 years. It was observed more commonly in first year of post transplantation . In this study most common bacterial infection observed was furunculosis in 6 patients (40%), followed by impetigo in 4 patients (26.6%) and cellulitis in 1 patients (13.3%). In a 43 year old post transplant diabetic patient both furunculosis and cellulitis were observed. The gram stain of pus material showed gram positive cocci in all the cases of furunculosis, impetigo and cellulitis. Erythrasma (Figure 3) was noted in 4 patients (26.6%) and the diagnosis was confirmed by coral-red flourescence in Wood's lamp examination (Figure 4).

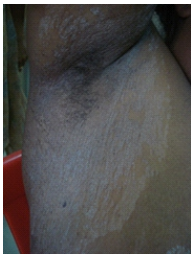

Figure 3: Erythrasma

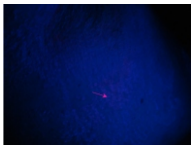

Figure 4: Woods Lamp Examination shows coral red fluorescence - Erythrasma

Drug induced changes were seen in 53 (66.25%) renal transplant patients, of whom 42 were males (79.2%) and 11 were females (20.7%). Their age ranged from 16 to 55 years with an average of 31.9 years. The various drug regimens used to induce immunosuppression was shown in Table 1. The commonly used regimen was combination of Cyclosporine, Azathioprine and Prednisolone in 49 (61.25%) patients, followed by combination of Tacrolimus, Mycophenolate mofetil and Prednisolone in 16 (20%) transplant recipients.

The commonest side effect observed was cushingoid facies in 23 patients (43.3%), followed by acneiform eruptions in 13 patients (24.5%) and striae in five patients (9.4%). Hypertrichosis over the face, chest, upper arm, and back was observed in four patients (7.5%) and these patients were on cyclosporine containing drug therapy. Gum hyperplasia was noted in five male patients (9.4%), who were all had treatment with cyclosporine. Three patients (5.6%) on cyclosporine developed hirsutism.

In this study, few miscellaneous cutaneous disorders were seen in five patients (6.25%). Keratosis pilaris was seen in one male patient who was on cyclosporine and prednisolone. Exaggerated insect bite allergy was noted in one HIV negative female patient. Fixed drug eruption was noted in one male patient and the probable drug was not known. One female patient developed lichen planus two years after the transplantation. A forty three year old male patient had classical scabies.

DISCUSSION

Renal transplant patients may present with various cutaneous lesions during the post transplant period. This study has been conducted to highlight the spectrum of skin lesions and to correlate the duration of the immunosuppressive therapy that predisposed to various dermatosis in RTR patients in a tropical environment. The study results show that infections were the most common cutaneous manifestation in renal transplant recipients. Among the infections, fungal infections were the most common (87.5%), followed by viral (28.75%) and bacterial infections (18.75%). These results were similar to the study conducted in India by Leni George et al[4] in 2010, and discordant with the study conducted in Tehran by Ghaninejad et al[5] which showed that viral infections (40%) were the commonest skin infection.

In this study, among the fungal infections, pityriasis versicolor (47.14%) being the most common infection followed by dermatophytosis (37.14%) and candidiasis (8.5%). The Leni George et al[4] (36.5%), Gulec et al[7] (36.3%) and Zamanian et al[6] (24.9%) studies also showed that pityriasis versicolor was the commonest fungal infection. The prevalence of pityriasis versicolor is higher in this study when compared to other studies like Chugh et al[8] (13.3%) and Koranda et al[9] (18%). The pityriasis versicolor lesions (Figure 5) were commonly noticed during the initial one year of post transplant period. The increased incidence of pityriasis versicolor in renal transplant recipients could be attributed to increased thickening of horny layer of skin, delayed desquamation of stratum corneum, overgrowth of Malassezia spp and mycelial shift due to immunosuppression and particularly with the use of systemic steroids.[10]

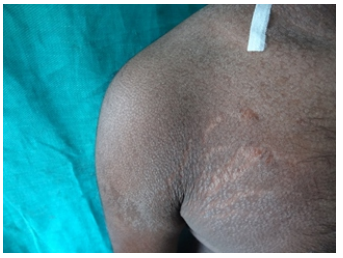

Figure 5: Striae with Pityriasis versicolor (achromic)

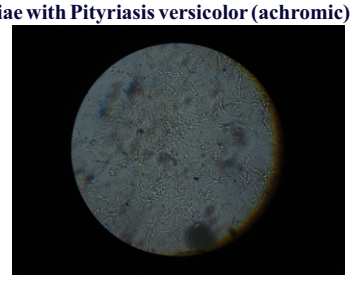

Figure 6: 10 % KOH examination shows short angulated aseptate hyphae with group of blastospores - Malessezia

Dermatophytosis (Figure 7) being the second commonest fungal infection in this study and the prevalence of dermatophytosis was about 37.14%, which was slightly lower than the study conducted by Selvi et al,[11] in which the prevalence of 42% was reported. In Leni George et al[4] study, dermatophytosis accounted for only 10% of total skin lesions which grossly differ from this study. All patients affected by dermatophytosis were males and none of the female was affected. This could be attributed to the large number of males were screened when compared with females. However, dermatophyte infection seems to be generally have less incidence in females as observed in various studies conducted.[11,12]

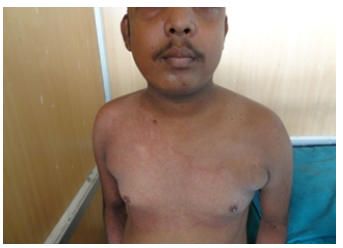

Figure 7: Cushingoid facies with Tinea corporis

In this study group dermatophyte infection frequently seen in 7 to 24 months of post transplant period which were similar to the results of Leni George et al[4] study, states that dermatophytosis were common in patients with post transplant period more than six months. Out of 26 patients with dermatophytosis 11 patients (42.3%) had chronic dermatophytosis inspite of adequate treatment. This incidence was almost equal to the observation noticed in Selvi et al study.[11]

The high prevalence and chronicity of the dermatophytosis observed in these patients could be due to the constant immunosuppression induced by the immunosuppresants. In addition, increased thickening of the horny layer of the skin and delayed desquamation of stratum corneum induced by the action of systemic steroids also plays significant role in the persistence of infection.[13] The commonest clinical type noticed in this study was tinea cruris (76.9%), followed by tinea corporis (69.2%) and tinea glutealis (46.1%). These results were comparable with the study conducted by Selvi et al[11].

The incidence of candidiasis in this study population was 8.5% and occurred commonly during the early (< 6 months) phase of post transplant period. These results were similar to the results of various studies like Ghaninejad et al[5], Sandhune et al[14] and Formicone et al.[15] The decreased incidence of candidiasis in renal transplant recipients compared to other fungal infection could be attributed to the factors like prophylactic antifungal therapy and asymptomatic nature of infection due to depressed immunity related deceased inflammatory response.[16]

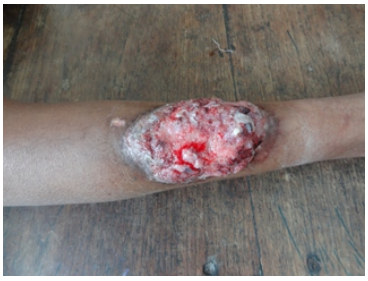

Figure 8 a): Phaeohypomycosis - ulceroproliferative growth

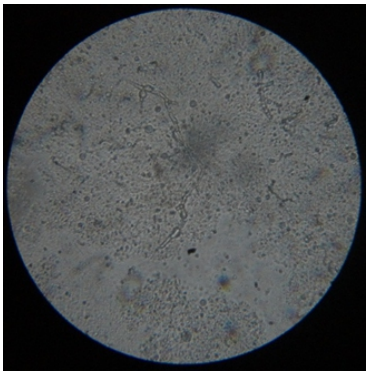

Figure 8 b): Phaeohypomycosis - Touch smear – 10% KOH examination septate moniliform hyphae

In this study phaeohypomycosis was occurred in 7.1% of patients with different clinical morphological patterns like multiple cysts, abscesses, ulceroproliferative growth (Figure 8a and 8b) and carbuncle, where as in Leni George et al[4] study one patient had a phaeohypomycotic cyst. There are few case reports from India on the presence of phaeomycotic cysts in renal transplant recipients.[17-18] Phaeohypomycosis was commonly seen in renal transplant patients with more than one year of post transplant period and prolonged immunosuppressive therapy.[19]

Herpes zoster (39.13%) was the most common viral infection observed in the study population. Leni George et al[4] study observed herpes zoster only in 7.5% patients. The immunosuppression induced reactivation of varicella-zoster virus occurred mainly between 7 to 24 months of post transplant period but according to Ghaninejad et al[5] study, the zoster lesions were commonly noted in early post transplant period (< 6 months). Verruca vulgaris (34.78%) was the second commonest viral infection noted in this study which is almost similar to the results of the study conducted by Ghaninejad et al[5]. In renal transplant patients the occurrence of warts increased with the duration of immunosuppression rather degree of immunosuppression[20] and frequently seen in patients on post transplant immunosuppressive therapy of more than one year duration.[21]

In this study the prevalence of herpes simplex infection was (13.04%) which was lower than the reported incidence of 35% in Koranda et al[9] study. Herpes simplex virus infections were substantially higher in the initial six months of post - transplant period. In one patient, lesions become ulcerated and persisted for about one month duration and completely healed after oral acyclovir therapy.

The prevalence of bacterial infection in this study was 18.7% and commonly manifested during the first one year of post transplant period. In this study, the prevalence of bacterial infection were little high when compared to Lugo-Janer et al[13] – 11%, Chugh et al[8] – 8.9% and Barba et al[22] – 3.5%. The commonest cutaneous lesion caused by bacterial infection was furunculosis (40%) followed by impetigo (26.6%) and the results (48.5% and 30% respectively) were comparable with Leni George et al[4] study. The probable reasons for decreased prevalence of bacterial infections in renal transplant individuals includes prolonged antibiotic therapy following transplantation and well preserved B lymphocyte function.

Drug induced cutaneous changes were more common in the initial one year of post transplant period. This may be attributed to the high dose of immunosuppressive drugs used during the early phase of post transplantation when the risk of rejection is higher.[4] Cushingoid facies (43.3%) (Figure 7) were observed to be the most common drug induced skin change, which is higher than the study results of Chugh et al (27.4%)[8] and Bencini et al (32.7%)[12]. Acneiform eruptions (24.5%) was the second common drug induced cutaneous change observed in this study and significantly higher in patients whose post transplant duration was less than six months and the results (24.6%) were similar to Leni George et al study[4] . These lesions were commonly observed with Cyclosporine, Azathioprine and Prednislone combination therapy because these drugs may act separately and/or synergistically on sebaceous gland[23]. The incidence of striae (9.4%) (Figure 5) in this study was high when compare to Leni George et al[4].

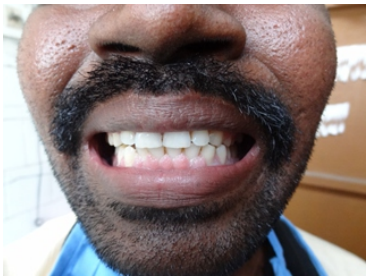

Figure 9: Gum hyperplasia

The incidence of gum hyperplasia (Figure 9) was found to be higher (6.25% vs 2.4%) and hypertrichosis was lower (5% vs 9.9%) when compared to Leni George et al study[4] and these changes also commonly noted in patients treated with cyclosporine[23] . Keratosis pilaris was noted in one male patient in this study and could be due to steroid and cyclosporine therapy[24]. In this study the drug induced changes showed a declining incidence as the transplantation interval lengthened as reported by Goldstein GD et al[25].

In this study , cutaneous malignancies were not seen which is similar to the observation by Leni George et al[4] study done in south India and the incidence of skin malignancies in Chugh et al[8] study were only 0.6%. Various other studies conducted in European countries showed that the incidence of skin cancer among kidney transplant individuals varied from 8% at 1 year to 44% at 15 year[26]

The cumulative effect of viral infections, prolonged immunosuppression and UV exposure has been thought to predispose renal transplant recipients for the development of cutaneous malignancies.[27] The increased level of melanin[28] and the pattern of melanosomal dispersion in individuals with skin phototypes V and VI are the important factors in decreasing the occurrence of skin malignancies by providing protection from the cutaneous effects of UV radiation and hence a very low incidence of malignant skin lesions in Indian renal transplant recipients.[28]

CONCLUSION

The prevalence of skin lesions in renal transplant recipients was found to be high. Among the screened patients, most common manifestation were fungal infections, followed by drug induced cutaneous changes, viral infections and bacterial infections. The superficial fungal infections like pityriasis versicolor, dermatophytosis and candidiasis were commonly encountered, of which pityriasis versicolor was the commonest, followed by dermatophytosis . The renal transplant recipients could be considered as a high risk group for the infection with malessezia and dermatophyte. Candidiasis was less frequently seen in kidney transplant patients. There is an increased incidence of phaeohypomycosis in renal transplant patients on prolonged immunosuppression. Herpes zoster and verruca vulgaris were the commonest viral infections seen in renal transplant patients. Among the bacterial infections , the commonest was furunculosis followed by impetigo.

In drug induced cutaneous changes, cushingoid facies were commonly seen, followed by acneiform eruptions and striae. Gum hyperplasia and hypertrichosis were commonly seen in cyclosporine containing drug regimen. The drug induced cutaneous changes were less common after one year of post transplantation. In the initial 6 months of post transplant period commonly observed cutaneous manifestations were candidiasis, herpes labialis, chickenpox , furunculosis and acneiform eruptions. Pityriasis versicolor lesions were frequently seen during the

7 to 12 months of post - transplant period. The dermatophytosis, herpes zoster and verruca vulgaris were commonly manifested between 7 to 24 months of post transplant period.

The anticipation of certain cutaneous lesions in the particular phase of post transplant interval and early diagnosis and treatment will improve the quality of life in renal transplant recipients.

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