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Original Article

Oral Manifestations of Allograft Recipients Before and After Renal Transplantation

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ABSTRACT. Renal transplantation is considered the best treatment option for patients with end-stage renal disease. In this study, the prevalence of oral lesions was studied in a cohort of renal transplant recipients before and after transplantation. Fifty-nine kidney transplant recipients were examined one week before and four months after transplantation. The information gathered included age, sex, smoking history, duration on dialysis, drugs and their doses. There were 41 males (69.5%) and 18 females (30.5%) with a mean age of 37 years. Before surgery, two patients had non-specific lesions and two other patients had leukoedema. Following transplantation, 24 patients (40.7%) did not have any specific lesion. In six patients, we observed non-specific erythematous lesions (10.2%). Other recorded observations are as follows: Gingival hyperplasia in five patients (8.5%), oral candidiasis of the erythematous type in five patients (8.5%), hairy leukoplakia in four patients (6.8%) and leukoedema in seven patients (11.9%). In our study patients, the prevalence of oral lesions increased after transplantation, although it was lower than that reported in other studies. This could be due to the differences in sample size, differences between Iranian race and other races and different pharmaceutical formulation of the drug produced in Iran.

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Introduction

Renal transplantation is one of the most effective methods for treating end-stage renal disease (ESRD). It can save the lives of patients and increase their life expectancy.[1] In recent decades, many new developments have emerged that have changed the post-transplan-

tation outcome. They include improved surgical methods, matching techniques and drug therapy against transplant rejection.[2,3] However, complications related to drug-induced immunosuppression are increasing. The immunosuppressive drugs commonly used are cyclosporine A (CyA), tacrolimus (Tac), sirolimus, azathioprine, mycophenolate mofetil (MMF) and corticosteroids.

In these patients, immunosuppression leads to the activation and proliferation of opportunistic factors such as viruses, bacteria and fungi. This results in many complications in different parts of the body, including solid tumors, hematological malignancies, post-transplant lymphoproliferative disorders, changes in the oral mucosa and changes in the minor and major salivary glands.[4,5] Apart from the systemic symptoms resulting from drug consumption, these patients also suffer from oral and dental problems that are directly related to the use of these drugs.[1,6,7]

Gingival hyperplasia, oral candidiasis and oral hairy leukoplakia are some problems these patients face. Gingival hyperplasia can interfere with speaking and chewing.[1,8] Oral candidiasis is the most prevalent oral fungal infection that has various manifestations.[8-10] Oral hairy leukoplakia is also one of the prevalent oral lesions in patients receiving immunosuppressive drugs.

Review of previous studies on oral manifestations in renal transplant recipients revealed that most of them were case–control studies. Considering the high error in such studies and the observation that the conditions for comparison are not similar between the case and control groups, we aimed to compare the oral manifestations of each patient before and after renal transplantation. Thus, each patient served as his own control subject, thereby reducing the possibility of error due to unknown confounding factors.

Patients and Methods

We selected 80 renal transplant recipients referred to the transplant department of the Nemazee Hospital, Shiraz, Iran. Informed written consent was obtained from each patient. One week before transplantation, complete oral examination was performed by specialists in oral medicine and oral pathologists, and the results were recorded. The oral mucosal surfaces were examined with a sterile dental mirror, gauze and examination stick. If any lesions were detected, para-clinical assessments (biopsy or smear) were made depending on the case.

Necessary data such as the patients' age, sex, drug history, duration on dialysis, smoking and blood urea were collected. Four months after renal transplantation, the same patients were referred to the Department of Oral Pathology, Faculty of Dentistry, Shiraz University of Medical Sciences. They were examined for any oral lesions and, additionally, the medications being taken and their dose was recorded. Ultimately, a list of observed lesions before and after transplantation was compiled.

Patients who had elevated blood urea levels and those who had rejected the allograft were excluded from the study. A total of 21 patients did not attend regular follow-up after the operation. Therefore, data obtained from the remaining 59 patients were evaluated using the Chi Square statistical test and SPSS software version 11.5. Data on age, sex, duration on dialysis and prevalence of the oral lesions were assessed.

Results

In this study, we evaluated 59 patients consisting of 41 males (69.5%) and 18 females (30.5%). The patients were 13–70 years old, with a mean age of 37 years. The duration on dialysis before transplantation was between one and 75 months, with a mean of 14 months; three patients had a history of smoking.

All patients were taking CyA 5 mg/kg (Abureihan LTD, Iran), MMF 2 g/day (Zahravi Pharmaceutical Company, Iran) and prednisolone (Ferdosi LTD, Iran) 30 mg initially and 5 mg at the time of the examination, daily. Before transplant surgery, two patients had non-specific lesions and two other patients had leukoedema. No specific lesion was seen in the

Table 1. Comparison of the prevalence of lesions before and 4 months after renal transplantation and its relationship with age and sex of the patients.

Type of lesion	Mean age (years)	Patients before surgery (%)	Patients after surgery (%)	Male patients (%)	Female patients (%)
Without lesion	36.8	55 (93.2)	24 (40.7)	18 (43.9)	6 (33.3)
Non-specific lesion	41.3	2 (3.4)	6 (10.2)	6 (14.6)	0
Gingival hyperplasia	24.6	0	5 (8.5)	4 (9.8)	1 (5.6)
Oral candidiasis	42.0	0	5 (8.5)	3 (7.3)	2 (11.1)
Hairy leukoplakia	40.5	0	4 (6.8)	1 (2.4)	3 (16.7)
Leukoedema	30.5	2 (3.4)	7 (11.9)	6 (14.6)	1 (5.6)
Leukoedema + non-specific lesion	50.0	0	3 (5.1)	1 (2.4)	2 (11.1)
Leukoedema + gingival hyperplasia	40.8	0	5 (8.5)	2 (4.9)	3 (16.7)
Total number	37.3	59 (100)	59 (100)	41 (100)	18 (100)

other patients.

In the post-operative examination, 24 patients (40.7%) were found to not have any specific lesion. In six patients, we observed non-specific erythematous lesions (10.2%). Other recorded observations were as follows: Gingival hyperplasia in five patients (8.5%), oral candidiasis of the erythematous type in five patients (8.5%), hairy leukoplakia in four patients (6.8%) and leukoedema in seven patients (11.9%). Each of the mentioned manifestations was observed individually; three patients (5.1%) had leukoedema accompanied by non-specific lesions and five other patients (8.5%) had leukoedema with gingival hyperplasia (Table 1).

Among the observed oral lesions, leukoedema had the highest prevalence (15 patients) and hairy leukoplakia had the lowest prevalence (four patients). Gingival hyperplasia was found in patients with the lowest mean age (24 years) and leukoedema with non-specific lesions in patients with the highest mean age (50 years) (Table 1). The overall prevalence of lesions was lower in patients less than 40 years of age (12 patients) compared with patients over 40 years of age (23 patients). However, no statistically significant difference was observed in this regard. Also, the most commonly observed lesion in females was hairy leukoplakia and, in males, it was leukoedema (Table 1). The co-occurrence of two associated oral lesions was more commonly seen in females. However, this was not statistically significant. No significant relationship was found between duration on dialysis and the prevalence of oral lesions.

Discussion

It is generally believed that oral lesions increase in patients receiving any type of organ transplantation. These lesions are generally related to drug-induced immunosuppression. The results of this study confirm this belief.

Broadly, six non-specific lesions were seen in the patients consisting of four erythemas, in which clinical and cytological examination did not detect any specific lesion, one geographic tongue and one minor salivary gland hyperplasia in the lower lip. These lesions were categorized in one group considering their low prevalence. Geographic tongue is migratory and is a prevalent lesion in the normal population (1–3% of the population).[10] Its manifestation could be coincidental and unrelated to drug-induced immunosuppression. Minor salivary gland hyperplasia has an unknown pathogenesis and some people believe that it can be the result of a trauma.[10] Because only one patient manifested this lesion, it might not be related to the consumed drugs but may be due to trauma. However, drug-induced immunosuppression could be involved in non-specific erythemas.

Gingival hyperplasia is another commonly observed lesion in these patients. This lesion is

caused by CyA and TAC that are administered to these patients.[1,9,11] It seems that these two drugs increase collagen and extracellular compounds in gingival tissues.[12,13] Torrezan and colleagues showed that the prevalence of gingival hyperplasia in 60 patients who had received CyA, was 52.8%.[11] In another study conducted by Estela and co-workers, the prevalence of gingival hyperplasia was 49% among 90 patients on treatment with CyA.[1] Gaston and colleagues reported the prevalence of gingival hyperplasia to be 22% in 159 patients.[14] Based on previous researches, the prevalence of this lesion has varied between 21% and 85%.[1,15]

In the present study, the prevalence of gingival hyperplasia (17%) was less than in the previous studies. Five of these patients (8.5%) had gingival hyperplasia alone, while five others had associated leukoedema in addition (8.5%).

After discontinuing CyA, gingival hyperplasia stops growing and it sometimes subsides, and replacing CyA with another drug can be beneficial.[16] If the patient's response allows drug replacement, we can substitute CyA with TAC.[8] The factors that influence the development and aggravation of gingival hyperplasia in patients on CyA are the dose of the drug, duration of medication, the patient's oral and dental status, genetic factors [16] and, possibly, the drug's chemical formulation. The relationship between a specific dose of the drug and the risk of causing or aggravating gingival hyperplasia is still controversial, but, according to some sources, doses over 500 mg can cause gingival hyperplasia in patients.[17] The average dose consumed by patients in this study was 5 mg/kg, which is the standard prescribed dose in most countries.[18]

If medication is mandatory, it is necessary to clean the mouth professionally and examine the mouth and control plaque consistently at home. Using anti-plaque agents such as chlorohexidin can be effective in preventing plaque formation and gingival hyperplasia. In some cases, systemic folic acid consumption has also been effective. Some researchers have indicated that after a short-term treatment with metronidazole and azithromycin, gingival hyperplasia caused by CyA subsided. Although the mechanism of action of these drugs is not yet clear, it seems that these antibiotics can prevent the reproduction of collagen fibers along with their antimicrobial characteristics. Azithromycin is also effective in treating gingival hyperplasia caused by nifedipine and phenytoin.[19]

Therefore, the severity of gingival hyperplasia is considerably related to the patient's oral health status.[11,12] Among the drugs causing gingival hyperplasia, CyA is the least related to the patient's oral health status; however, plaque and calculus control have considerable effect during consumption of this drug.[10] Lack of sufficient and suitable oral health is an important aggravating factor for gingival hyperplasia.

Based on studies performed, gingival hyperplasia is expected to commence 1–3 months after the start of CyA therapy.[8] The patients of this study were examined four months after this drug was started. Therefore, it can be conclu-ded that the time chosen for examining this lesion was suitable, but, with the passage of time, the lesion's prevalence also increases.

Considering the dose of medication, duration of consumption and the fact that the patients did not reject the renal allograft until the time of examination and even after that, and although most patients had poor oral health, we might be able to hypothesize that the drug manufactured in Iran has a suitable formulation and is prescribed to patients in a suitable dose, which can ensure the least amount of gingival side-effects compared with its foreign brands. Of course, this hypothesis needs further assessment.

Researchers have suggested that the susceptibility to gingival hyperplasia due to CyA depends on a specific type of HLA, while other types of HLA help in protecting against hyperplasia. Whether such a relationship exists with other drugs that cause hyperplasia or not is still unknown.[8,10,12] Considering this effect, we can perhaps relate the lower prevalence of gingival hyperplasia in Iranians to the status of their immune system or genetic factors. This

issue could be addressed in future studies.

Another lesion seen in the studied patients was candidiasis. This lesion was diagnosed in the patients based on clinical examination, cytological smear and microscopic evaluation. Oral candidiasis is an opportunistic infection accompanied by local and systemic risk factors.[20-22] One of the causes of candidiasis is immunosuppression. In our study, the prevalence of this lesion was 8.5% (five people). In a study performed by Lopez and colleagues, the prevalence of candidiasis was 7.4%.[20] In another study by Almohaya and co-workers, the prevalence of this lesion was 15.5%,[13] and Estela et al reported a prevalence of 18.7% for candidiasis in allograft patients.[1] Gulec and colleagues also showed a prevalence of 26%. The prevalence rates reported in these studies were higher than the results obtained in this study.[23] A study performed by Gaston and co-workers reported a prevalence of 5.6% for candidiasis,[14] which is lower than the result of this study. The reason could be the difference in the number of studied patients as well as the differences in diagnostic criteria. Consistent with other studies, the type of candidiasis observed in the patients of this study was the erythematous type.[13,24,25]

The cause of candidiasis in these patients was immunosuppression due to consumption of drugs, especially corticosteroids. As individuals age, the immune system naturally weakens;[26] therefore, the possibility of candidiasis is higher in the elderly.[12] In this study, candidiasis was seen more commonly in patients over the mean age of 40 years; thus, age could be influential in this regard.

Hairy leukoplakia was another lesion observed in these patients. This lesion is generally seen in patients infected by the human immunodeficiency virus (HIV),[14,26] and it has a prevalence of 9–20%.[23,26] It is caused by the Epstein Barr virus (EBV).[12,18] The occurrence of this lesion in patients who have undergone renal transplantation shows that this lesion is not specific to HIV-infected patients; it can be implied that drug-induced immunosuppression is a causative factor in the occurrence of this lesion.[18] In this study, oral hairy leukoplakia was seen in four patients (6.8%) according to clinical criteria. In Almahaya, Estela and Gaston's studies, the prevalence of hairy leukoplakia was 15.5%, 13% and 11.3%, respectively.[1,13,14] The difference in prevalence rates could be due to the number of studied patients in the present study compared with others, and also the differences in the diagnostic criteria.

Another lesion observed in this study was leukoedema. Leukoedema is a normal variation in the oral mucosa of healthy individuals and does not indicate a pathologic condition. This condition is often bilateral in the buccal mucosa and, sometimes, it is seen on the borders of the tongue. Leukoedema often fades after stretching the mucosa, only to reappear later.[10] This lesion was observed more after renal transplantation. The prevalence of leukoedema increases with age, but, according to previous studies, it has no significant relationship with gender.[27] In this study, six cases of individual leukoedema were seen in males and one case in a female. Six patients were less than 40 years of age and one patient was over 40 years. The cause of this lesion is debatable and should be assessed in future studies.

According to the results obtained in the present study, the prevalence of oral lesions increases after renal transplantation. We suggest that patients should undergo detailed oral examination alongside routine post-operative examinations. The occurrence and severity of oral lesions such as gingival hyperplasia and candidiasis in renal transplant recipients is influenced by their oral health status. Therefore, it is advised to give these patients supplementary oral and dental health training in order to prevent the consequences of gingival hyperplasia such as mental strain caused by cosmetic problems and disturbances in chewing and eating. Proper diagnosis will help in allowing the physician to replace the drug in case gingival hyperplasia occurs and impart necessary supplementary oral health training for reducing the severity of the lesions.

One of the other lesions seen in the present study is oral candidiasis. Because the antifungal drug nystatin is not used regularly in transplant recipients, we suggest that it should

be used on a regular basis in patients who have this lesion or for prophylaxis.

In conclusion, our study shows that the prevalence of oral lesions increases after renal transplantation and special care should be imparted to relieve the patient's oral discomfort. However, the prevalence of lesions was lower in our study compared with other related studies. This can be due to the sample size, race or differences in drug formulation.

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Conflict of interest: None

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