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Faustino, Isabel Schausltz Pereira; Fernandes, Diego Teztner;
Santos-Silva, Alan; Vargas, Pablo Agustin; Lopes, Marcio Ajudarte
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Oral carcinoma development after 23 years of renal transplantation

Isabel Schausltz Pereira Faustino^a , Diego Teztner Fernandes^a ,
Alan Roger Santos-Silva^a , Pablo Agustin Vargas^a , Marcio Ajudarte Lopes^a 

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ABSTRACT

Renal transplant patients are treated with immunosuppressive drugs that decrease the effectiveness of the immune system, making them more prone to developing cancer. Skin and lip carcinomas are common malignancies encountered after transplantation, whereas oral carcinomas are rare. We report the case of a 51-year-old female Caucasian patient, with no history of smoking, who presented white lesions on the tongue and an ulcerated lesion on the lower lip beginning 4 months prior. Diagnosis of squamous cell carcinoma for both lesions was made following incisional biopsies. Interestingly, the patient reported a renal transplantation 23 years prior, and was maintained on a combination of cyclosporine, mycophenolate sodium and prednisone. The patient also presented a history of several basal and squamous cell carcinomas on sun-exposed areas of the skin. Both lesions were surgically excised. No sign of recurrence or new lesions in the oral cavity have been observed; however, new skin lesions are frequently diagnosed. This case report highlights that oral cancers may occur in transplant patients in the absence of classical risk factors. Thus, clinicians must be aware of the importance of thorough oral examination in transplant patients in routine follow-up.

Keywords

Lip neoplasm; Tongue neoplasm; Mouth neoplasm; Kidney transplantation

INTRODUCTION

Renal transplantation is the treatment of choice for patients with end-stage renal disease, which may improve their survival rate and quality of life.^{1,2} However, renal transplantation also increases the risk of cancer,³ with a 5% to 6% increase in the incidence of cancer when compared to the general population.⁴ This can be attributed to the alteration of immune surveillance mechanisms due to the chronic use of immunosuppressive therapy and infection by oncogenic viruses.⁴⁻⁶ About 13% of transplanted patients develop cancer;⁷ however, the risk of malignancies is not the same for all types of cancer.⁸

Cancers of the skin and lip have been described to occur at a higher incidence⁹ among transplanted

patients; however, the incidence of oral carcinomas, especially in the tongue, is scarcely reported in the literature.¹⁰⁻¹⁴ The current report presents the case of a renal transplant patient who developed multiple carcinomas in the skin with synchronous development of lip and tongue carcinomas, highlighting the importance of oral examination in the follow-up of these patients.

CASE REPORT

A 51-year-old female patient was referred for evaluation of white lesions on the tongue and ulcerated lesions on the lower lip that had developed over the past

^a University of Campinas, Piracicaba Dental School, Oral Diagnosis Department. Piracicaba, SP, Brazil.

4 months. She denied smoking and consuming alcohol. She had been diagnosed with systemic erythematous lupus (SLE), and lost renal function as a result of lupus nephritis. The patient had undergone renal transplantation 23 years prior, and was on continuous post-transplant immunosuppressive therapy with a combination of cyclosporine, mycophenolate sodium and prednisone.

On physical examination, numerous skin scars were observed due to the surgical removal of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) that developed during immunosuppressive therapy, especially on the upper limbs and face. The lower lip showed an erythematous area with central ulceration. On intraoral examination, a heterogeneous and slightly corrugated white plaque was observed on the ventral surface of the tongue (Figure 1).

Incisional biopsies of the lip and the tongue were performed under local anesthesia. The diagnosis of SCC was established, and the patient was referred to a head and neck surgeon who surgically removed both lesions (Figure 2).

After 5 years of follow-up, the patient developed SCC on the forearm, hand, neck, finger, scalp, cheek, leg, nose and temporal region. BCCs developed on the nose, thorax, lower eyelid and upper back.

All tumors that had presented since renal transplantation are listed in Table 1.

The patient is on regular follow-up, and no signs of recurrence or new primary tumors in the oral cavity have been observed. However, the patient has undergone removal of several carcinomas (BCCs and

SCCs) of the skin, and future biopsies for new lesions on the nose and forehead are scheduled. The patient signed a declaration of consent in accordance with the standard institutional protocol.

DISCUSSION

Renal transplantation is the ultimate treatment option for kidney failure, aiming to improve the patient's quality of life. However, there are some complications related to immunosuppressive maintenance therapy, such as increased susceptibility to infections and a higher risk of cardiovascular disease and malignancies.¹⁵ The development of cancer is a significant complication of renal transplantation. The higher likelihood of developing cancer⁴ can be attributed to the maintenance immunosuppressive therapy.^{16,17}

Some immunosuppressive drugs may potentiate the action of carcinogens, independent of their effects on immune cells,¹⁸ while others are related to cellular changes and the development of malignancies. Cyclosporine inhibits DNA repair and apoptosis in human keratinocytes exposed to UVB radiation,^{19,20} and prednisone may be associated with a higher probability of malignancy by diminishing DNA repair mechanisms.²¹ Studies^{22,23} suggest that immunosuppressive agents may be involved in the activation of mechanisms of the tumor growth, such as transforming growth factor alpha and vascular endothelial growth factor. Moreover, withdraw of immunosuppressive therapy in case of transplantation failure is associated with an immediate reduction in the risk of some cancers, such as lip cancer, melanoma and non-Hodgkin's

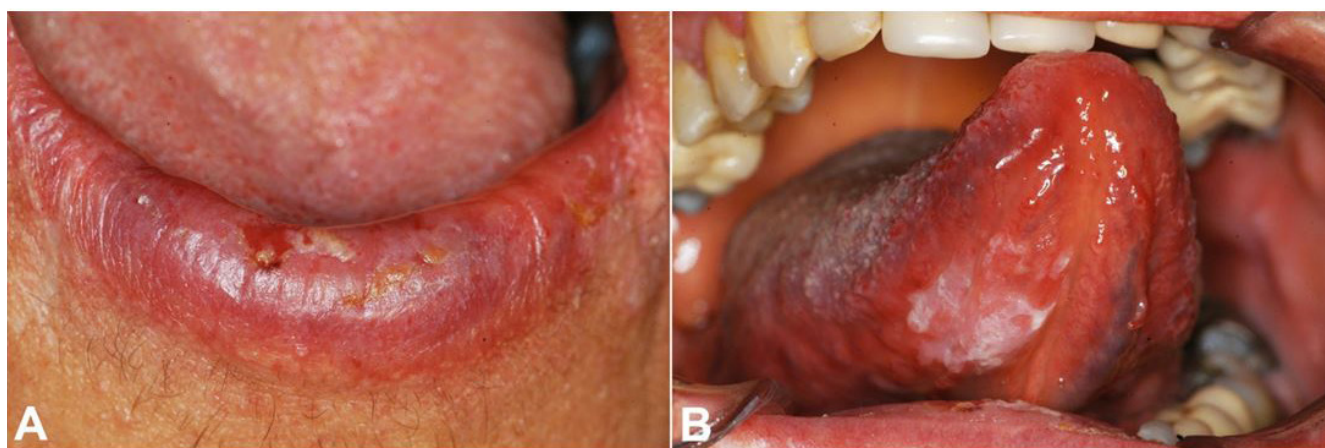


Figure 1. Gross view of the lesions at the time of diagnosis. **A** - Ulcerated lesion on the lower lip. **B** - White patch on the ventral surface of the tongue.

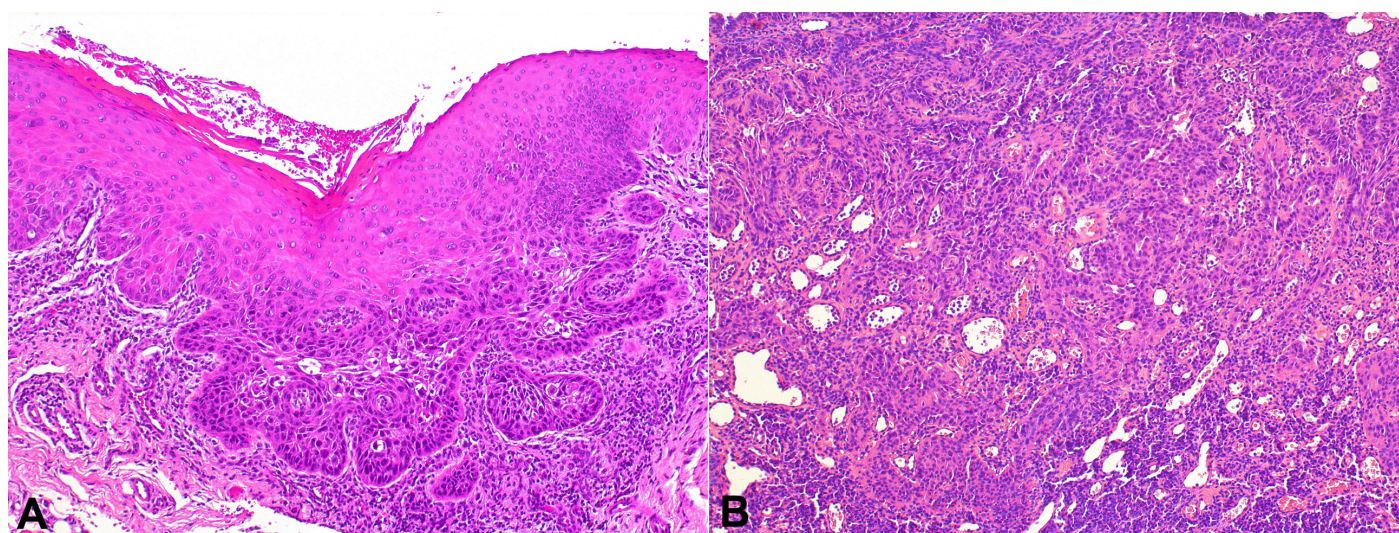


Figure 2. Histopathological aspects of squamous cell carcinoma. **A** - Microinvasive tumor of the tongue. **B** - Tumor cells in the connective tissue of the lower lip.

Table 1. All tumors presented by the patient from renal transplantation to the time of diagnosis of oral lesions

Number of the tumor	Histopathologic Diagnosis	Location	Years after transplantation
1	SCC	Face	8
2	BCC	Skin of lower lip	11
3	BCC	Skin of lower lip	11
4	SCC	Skin of lower lip	12
5	BCC	Pre auricular	15
6	BCC	Parietal region	15
7	SCC	Occipital region	15
8	SCC	Skin of lower lip	15
9	SCC	Dorsal of hand	15
10	SCC	Scalp	16
11	SCC	Skin below the eye	17
12	SCC (<i>in situ</i>)	Nose (right)	17
13	BCC	Nose (left)	17
14	SCC	Ventral tongue	18
15	SCC	Lower lip	18
16	SCC (<i>in situ</i>)	Scalp	18
17	SCC	Scalp	18
18	SCC	Right hand	19
19	SCC	Neck	20
20	SCC	IV finger	20
21	SCC	Scalp	21
22	SCC	Cheek	23
23	BCC	Nose	23
24	BCC	Forehead	23
25	SCC	Leg	23
26	BCC	Thorax	23
27	SCC	Left arm	23
28	BCC	Lower eyelid	23
29	SCC	Nose	23
30	BCC	Upper back	23
31	SCC	Temporal region	23

SCC: squamous cell carcinoma; BCC: basal cell carcinoma.

lymphoma.^{23,24} The synergic effect between UV radiation and immunosuppressive therapy can be observed in lesions related to sunlight exposure, such as skin and lip cancers.²⁵ In the present report, the patient was under continuous cyclosporin treatment for 23 years in association with mycophenolate sodium and prednisone, and she developed lip and tongue SCCs in addition to multiple skin carcinomas.

Systemic erythematosus lupus has been associated with an increased risk of cancer. Nevertheless, the specific cause is not clear, and may be attributed to dysregulation of the immune system or a side effect of the immunosuppressive medication used for treatment.²⁶ A recent systematic review and meta-analysis²⁷ on the risks of cancer development in SLE patients concluded that SLE is associated with an increased risk of cancer in general, particularly hematological, reproductive, digestive and respiratory cancers in women and men. However, lip and tongue cancers were not cited by this study. On the other hand, a clinical case of tongue cancer has been reported in the English literature in a pregnant woman with SLE, who had classic high-risk habits for the development of oral carcinoma, which makes the association with lupus questionable.²⁶

In contrast to SCCs, BCCs are the most common type of skin cancer worldwide. However, skin SCCs can occur up to 25 times more frequently in transplanted patients.²⁸ The association between immunosuppression and sun exposure can be evidenced in our case, as our patient developed multiple skin carcinomas in sun-exposed areas, especially in the head and neck region.

Lip cancer development has also been described as a common consequence of renal transplantation.^{18,25,29,30} Lip carcinoma is more common in Caucasians chronically exposed to the sunlight, and almost all lip SCCs are associated with areas of actinic cheilitis.^{18,25,31,32} The patient in our case report presented fair skin and a history of sunlight-exposure with a delayed habit of UV protection. The combination of these factors with immunosuppressive therapy seems to have contributed to the development of these tumors. Interestingly, although lip SCCs are typically associated with severe actinic cheilitis features, such as red spots, white plates, hardening and loss of vermilion border definition, the current patient only had mild actinic cheilitis.

Although SCC of the tongue is the most frequent oral malignancy in the general population, it seems to be rare in renal transplant patients.¹⁰⁻¹⁴ While tobacco and alcohol consumption are the most important risk factors for these lesions, diet, nutrition, viruses and genetic predisposition have also been associated with SCC.³³ In general, oral SCCs are more frequently observed in adult male patients with a heavy smoking habit and alcohol consumption.³⁴ The profile of risk factors for oral SCCs in transplanted patients are different from those of the general population, and to the best of our knowledge, all reports in the English literature do not resemble the traditional pattern of oral SCCs (Table 2).

The present report is the only case of a tongue SCC in a female transplanted patient without classical risk factors (tobacco and alcohol) published in the literature. In addition, this case presented a longer post-transplant period for tongue SCC development (23 years) compared to the average of 9.4 years among the reported cases.

Table 2. Reports on oral SCCs in transplanted patients published in the English literature and their respective findings

Author	Gender	Age (y)	Time since renal transplantation (y)	Tobacco use	Alcohol abuse	Immunosuppressive drugs
Lee & Gisser ¹⁰	Male	26	9	No	No	Azt / Pred
	Male	55	7	No	No	Azt/ Cyc/ Pred
Meng ¹¹	Male	40	11	No	No	Azt/ Cyc/ Pred
	Male	52	11	No	No	Azt/ Cyc/ Pred
Zhang et al. ¹²	Male	65	8	No	No	Azt/Cyc/Pred
Malleshappa ¹³	Male	30	9	No	No	Azt/ Cyc/ Pred
Prakash ¹⁴	Male	46	11	No	No	Azt/ Cyc / Steroids
Current case	Female	51	23	No	No	Cyc / Pred / Myc/

Azt: Azathioprine; Pred: Prednisolone; Cyc: Cyclosporine; Myc: Mycophenolate sodium; y: year.

After renal transplantation, malignant diseases are more difficult to control, and the surgical principles for early-stage tongue cancer in these cases are similar to advanced-stage cases due to the low immune states that facilitate tumor metastasis and severe infection after surgery.¹¹ The reported patient showed no signs of metastasis or local recurrence, which may be explained by the early diagnosis and, consequently, better prognosis.

In conclusion, Caucasian transplant patients with a history of sunlight exposure have a higher propensity to develop lower lip and skin cancer. In addition, although rare, oral cancer can also be observed in this group of patients, even after a long follow-up period. Thus, clinicians must be aware of the necessity and importance of oral examination of transplanted patients, and a regular and close follow-up should be enforced.

The patient has signed the consent declaration as to the Institutional standard protocol.

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Correspondence

Márcio Ajudarte Lopes

Departamento de Diagnóstico Oral - Semiologia - Faculdade de Odontologia de Piracicaba (UNICAMP)

Av. Limeira, 901 – Piracicaba/SP – Brazil

CEP: 13414-903

Phone: +55 (19) 2106-5320

malopes@fop.unicamp.br