Early diagnosis of lip cancer preceded by a persistent actinic lesion in a kidney transplant patient: a case report

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Lip cancer is 65 times more likely to occur in kidney transplant patients than in members of the general population. Immunosuppression drugs taken by the transplant patients have been associated with this increased occurrence. This case report shows the progression from actinic cheilosis to squamous cell carcinoma (SCC) in the lower lip of a 58-year-old man receiving immunosuppressive therapy 9 years after undergoing a kidney transplant. Earlier incisional biopsies had resulted in a histological diagnosis of actinic cheilosis. However, the last incisional biopsy showed histological results compatible with SCC, and oncological surgery was performed. Eight months post-surgery, the patient was free of cancer and metastasis. Frequent dental follow-up visits allowed for the early diagnosis, proper treatment, and an improved prognosis for this patient.

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One well-established complication of organ transplantation is an increased risk for various types of cancer. Kidney transplant patients have a greater risk of developing lip cancer, nonmelanoma skin cancer (NMSC), anogenital neoplasias, and non-Hodgkin lymphoma compared to the general population. Immunosuppressive therapy—administered to prevent rejection of the transplanted organ—has been cited as a factor in the increased incidence of these diseases.

Squamous cell carcinoma (SCC) is a malignancy that is most commonly found in the head and neck region. The incidence of SCC in the lower lip is up to 65 times higher in kidney transplant patients compared to the general population. The transitional epithelium between the lip mucosa and the skin makes this area vulnerable to carcinogenic factors such as ultraviolet (UV) radiation, either UVA (longwave) or UVB (shortwave). Actinic cheilosis presents as a scaly lesion on the lip vermilion and is caused by damage from UV radiation. The progression of an actinic lesion to SCC has been shown to be potentiated by certain immunosuppressive drugs.

The progression from actinic lesions to SCC involves a number of risk factors. Major risk factors include the intensity of sun exposure (influenced by geographic latitude, occupational habits, and skin color), age, and genetic predisposition; minor risk factors include immunosuppression (as occurs in organ transplantation), tobacco, alcohol, and human papilloma viruses (HPVs). Long-term administration of immunosuppressive drugs, combined with exposure to carcinogenic factors, result in immune deregulation and DNA damage. The type, dose, and duration of...
the administration of immunosuppressive drugs can affect the risk of cancer. One group of immunosuppressors are calcineurin inhibitors, such as tacrolimus and cyclosporine; they elevate the risk of cancer considerably (especially cyclosporine) compared to other classes of drugs.8,9

This article presents a case involving a kidney transplant patient who received an early diagnosis of lower lip SCC. Frequent follow-up visits enabled the dentist to employ proper treatment for the lesion, thus providing an improved prognosis.

**Case report**

A 58-year-old man who had received a kidney transplant 9 years earlier due to lupus nephritis was referred from the Nephrology Service of the Federal University of Ceara Hospital, Brazil, to the university’s School of Dentistry for treatment. The patient had received immunosuppressive therapy since the transplant, taking cyclosporine (originally 300 mg, now 75 mg), mycophenolate mofetil, and prednisone (originally 20 mg, now 5 mg). The patient stated at anamnesis that he was an agriculturist and a non-smoker who used to work under intense exposure to the sun. During clinical evaluation, an ulcerative recurrent lesion (approximately 2 cm in diameter) exhibiting some healing areas was observed on the lower lip. In addition, leukoplakic lesions were seen throughout the lower lip, as was blurring of the margin between the vermilion zone and the cutaneous portion of the lip (Fig. 1). After hematological evaluation, an incisional biopsy was performed, leading to a histological diagnosis of actinic cheilosis (Fig. 2). An excisional biopsy confirmed the histological diagnosis. The patient was encouraged to use lip balm with sunscreen, and to decrease his exposure to the sun, thus preventing further damage; at that time, a follow-up regimen was established. In the 20 months postbiopsy, the patient had 2 recurrences (followed by healing) over a period of 4 months, which were associated with unprotected exposure to the sun (Fig. 3). A third recurrence (6 months after the first) persisted for more than 15 days (Fig. 4). An incisional biopsy led to a histological diagnosis of well-differentiated, superficially invasive SCC (Fig. 5 and 6). Using a wide “V” excision, the tumor was removed from the lip. The resection margins were histologically tumor-free. After SCC was diagnosed, the
Long-term use of immunosuppressive regimens is also associated with an increased risk for cancer; Moloney et al found a peak incidence of skin cancer 8 years after kidney transplantation. In the present case, lip cancer was the first malignant lesion to appear. The patient’s triple-agent immunosuppressive regimen (the same since transplantation) included cyclosporine, which is strongly related to tumor development. Despite reducing the patient’s dosage regimen of immunosuppressive drugs, lip cancer appeared after 9 years of treatment.

As stated before, the incidence of SCC of the lower lip in kidney transplant patients varies, but can be 65 times greater than the risk among the general population. It is probable that lip cancer has similar risk factors to those of skin cancer. The anatomical position of the vermilion of the lower lip—in addition to the transitional epithelium that exists between the lip mucosa and the skin—makes this area vulnerable to a distinct combination of exposures with well-known carcinogenic potential. Important etiological factors (such as tobacco and alcohol use, HPVs, and UV radiation) can damage epithelial DNA. In addition, both UVA and UVB are responsible for the breakdown of vitamin A, local immunosuppression, mutagenic changes to the DNA, and mutations in the epithelial p53 tumor-suppressor gene that inhibits apoptosis. Immunosuppressive drugs intensify these effects and jeopardize important DNA repair pathways.

The clinical and histological aspects of SCC of the lower lip are not limited to kidney transplant patients. Nevertheless, patients with NMSC show an increased number of immunohistochemical markers for tumor angiogenesis (that is, microvesSEL density and capillary proliferation index) compared to immunocompetent individuals. Lip cancer associated with kidney transplantation occurs at an earlier age compared to the general population. Lip cancer in the general population is more prevalent in male Caucasians, and individuals exposed to high doses of solar radiation. The gender difference may be due to the fact that many women wear lipstick, offering them some protection from UV radiation.
Since the patient in the present case was at high risk for developing lip cancer, he underwent follow-up appointments every 3 months after actinic cheilosis was first diagnosed. At every appointment, the need for sun protection was reinforced. The recurrences were related to the patient’s return to work, which required intense solar exposure, even though the patient was aware that such exposure was contraindicated. The recurrent lip lesions were monitored weekly and an early sign of malignancy—the lesion’s failure to heal—led to an incisional biopsy during the last recurrence.

Conclusion
Due to the high risk of malignancies, kidney transplant patients must undergo routine examinations and long-term frequent follow-ups by medical and dental teams. The follow-up in the present case— involving careful examination of the skin and oral regions—made early diagnosis of potentially malignant and malignant lesions possible. Modifying the immunosuppressive regimen after cancer is diagnosed (by utilizing sirolimus or everolimus instead of cyclosporine or tacrolimus) may be a safe alternative to reduce the risk of de novo cancer or tumor recurrence.

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References