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Squamous cell carcinoma in a kidney transplant recipient after 26 years

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ABSTRACT

Kidney transplantation is the preferred treatment for patients with end-stage renal disease. However, the immunosuppressive therapy used to prevent graft loss can lead to various complications, including cancer, which is the most severe. This paper reports a clinical case of squamous cell carcinoma that developed in the oral cavity of a kidney transplant patient who underwent the procedure 26 years ago and did not present classic risk factors, such as smoking and alcohol consumption, for the development of the lesion. The lesion on the gingival ridge was reddish in color, had a granulomatous surface, and was firm on palpation. It extended from the lower left incisors to the molars. Additionally, there was an increase in lymph nodes in the ipsilateral submandibular region. According to the literature, malignant neoplasms can take an average of 20 years to develop after transplantation, with the risk increasing considerably to over 45%. The oral cavity is a predilection site in the head and neck region, and many lesions are associated with human papillomavirus (HPV), an oncogenic virus whose infection can be potentiated by chronic immunosuppression in transplant patients. In addition, some drugs, regardless of their immunosuppressive mechanisms, have the ability to induce carcinogenesis, with cyclosporine and azathioprine being clear examples. Therefore, we must always pay attention to this group of patients because we know that they are more susceptible to oral cancer, even in the absence of classic risk factors.

1. Introduction

Kidney transplantation is the gold standard for treating patients with end-stage renal disease, and its success is due in part to the use of immunosuppressive therapies that prevent potential graft loss, thereby improving patients' quality of life and survival compared to hemodialysis [1,2].

Despite the administration of contemporary immunosuppressive agents, recipients of solid organ transplants remain susceptible to significant complications [2]. These complications encompass a spectrum of adverse outcomes, notably including cardiovascular diseases, infections, and cancer. The latter, in particular, emerges as a predominant cause of mortality in these patients, exhibiting an incidence ranging from 3 to 10 times higher when juxtaposed with the general population [3,4].

The association between immunosuppressive therapy and the development of cancer is well established in the literature. Chronic use of immunosuppressive drugs leads to a compromised immune system, impairing the immune response and reducing tumor immunosurveillance, which in turn increases susceptibility to cancer [1,5].

Presently, there exists a notable prevalence of Kaposi's sarcoma, non-melanoma skin cancers, lip cancers, and lymphoproliferative disorders

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linked to oncogenic viruses following kidney transplantation [3]. In the context of head and neck cancer, the documented risk for occurrence in these patients is reported to be 1.6 times higher [5,6].

Despite the increased incidence of head and neck cancer in solid organ transplant recipients, instances of such lesions specifically localized in the oral cavity remain infrequent, particularly in the absence of conventional risk factors such as smoking and alcohol consumption. In light of this, the aim of this paper is to present a clinical case involving a kidney transplant recipient who, after a span of 26 years, manifested the development of squamous cell carcinoma on the alveolar ridge. This case underscores the significance of diligent dental monitoring for individuals undergoing organ transplantation, emphasizing the crucial role of preventive measures in mitigating the risk of oral malignancies in this specific patient population.

2. Case report

A 58-year-old male patient was referred for the assessment of a gingival lesion with a two-month progression. He reported pain in the region, particularly during chewing and swallowing, accompanied by spontaneous bleeding. He didn't use tobacco or alcoholic beverages and reported a history of systemic arterial hypertension, diabetes mellitus, and a kidney transplantation, performed 26 years ago, and is currently being followed. Current medications included hypoglycemic agents, antihypertensives, lipid-lowering drugs, and immunosuppressants (cyclosporine and azathioprine).

Upon clinical examination, a sessile nodular lesion was identified along the gingiva, from the left mandibular incisors to the molars, displaying a reddish hue and featuring a granulomatous surface (Fig. 1). Extraoral palpation revealed enlarged lymph nodes in the left submandibular region.

For systemic evaluation of the patient, blood count, coagulogram, glycemia, glycated hemoglobin and CRP (C-reactive protein) were obtained and were within normal limits. An incisional biopsy was then performed under local anesthesia, and histopathological analysis revealed the presence of squamous cell carcinoma.

The patient was referred to a specialized oncology service and subsequently underwent surgery for tumor removal and neck dissection. Subsequently, the patient received full-dose radiotherapy in accordance with the recommended protocol for head and neck cancer. Presently, the patient is undergoing regular medical and dental monitoring, with no reported recurrence.

3. Discussion

This report describes the clinical case of kidney transplant recipient who, after 26 years of immunosuppressive drug use, developed squamous cell carcinoma in the oral cavity. Notably, the patient did not exhibit common risk factors such as smoking or alcohol consumption, which are typically associated with the onset of this lesion. According to the literature, the average time for the development of malignant neoplasms in transplant patients ranges from 3.9 to 7.3 years, nevertheless, after 20 years, the risk of developing a malignant neoplasm increases significantly, exceeding 45% [1,5,7,8].

According to Mowery et al., 2019 [6]a history of solid organ transplantation was a significant predictor of an increased incidence of head and neck cancer, with relative risks ranging from 1.8 for thyroid to 2.9 for salivary glands. In addition, worse overall survival was also observed in these patients.

A smaller study by Alsidawi et al., 2017 [7] found that in the head and neck region, the primary site of greatest involvement of malignant neoplasms after renal transplantation was the oral cavity, followed by the oropharynx. In the oropharynx, 75% were immunohistochemically positive for P16, suggesting an association with human papillomavirus (HPV). This association has been frequently reported in the literature in the general population, but in transplant patients, chronic immunosuppression may potentiate infections with oncogenic viruses such as HPV, Epstein-Barr virus (EBV), herpes virus type 8, human T-cell lymphotropic virus-1, human polyomavirus, and hepatitis B and C viruses [1,9].

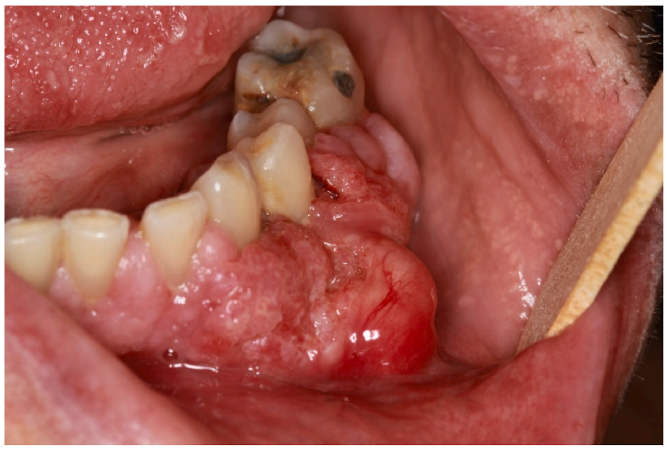

Fig. 1. Squamous cell carcinoma of the gingiva. Sessile nodular lesion at the gingival margin, reddish in color with granulomatous surface, extending from the lower left incisors to the molars. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

In addition, some drugs, regardless of their immunosuppressive mechanisms, have the ability to induce carcinogenesis [10]. In the case of our patient, the use of azathioprine and cyclosporine (a calcineurin inhibitor) was noted. Studies indicate that both these drugs can exert a direct oncogenic influence. Cyclosporine, for instance, inhibits apoptosis and DNA repair, while also stimulating the production of transforming growth factor beta (TGF-beta) and vascular endothelial growth factor (VEGF), thereby facilitating the development of malignant neoplasms and metastases. Azathioprine, on the other hand, is known for its capacity to inhibit and augment the damage caused to DNA by ultraviolet (UV) rays [1].

Comprehending this information elucidates that carcinogenesis in immunosuppressed patients is a multifactorial process. Nevertheless, it is imperative to acknowledge the primary factors contributing to the development of head and neck cancer, namely the consumption of tobacco and alcoholic beverages [8]. Regrettably, the majority of studies conducted on transplant patients with head and neck cancer faced challenges in segregating smokers and alcoholics from the non-smoking, non-drinking population. Even when such distinctions were attempted, the sample size of non-smokers often remained insufficient for a thorough investigation. Hence, continuous attention to this patient group is essential, given their heightened susceptibility to oral cancer, even in the absence of conventional risk factors.

CRediT authorship contribution statement

Carolina da Silva Nunes: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Andreia Bufalino:** Supervision, Writing – review & editing. **Cláudia Maria Navarro:** Visualization, Writing – review & editing. **Jorge Esquiche León:** Supervision. **Héric de Souza Camargo:** Writing – original draft. **Elaine Maria Sgavioli Massucato:** Conceptualization, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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