

Well-differentiated Squamous Cell Carcinoma and a Foreign Body Reaction – A Case Report

Martins Allisson FL, Arantes Diego AC, Bellotti Alexandre, Mendonça Elismauro F

Department of Stomatologic Sciences, Federal University of Goiás, Goiânia, GO, Brazil

Abstract

Squamous cell carcinoma (SCC) is a common malignancy that can affect the oral cavity. This neoplastic lesion is characterized by the presence of malignant squamous epithelial cell nests, keratin pearls, individual cell dyskeratosis, and atypical cells surrounded by a chronic inflammatory infiltrate. An uncommon event in this inflammatory infiltrate is the presence of multinucleated giant cells (MGCs) in the SCC stroma, and hence the clinical relevance and the true nature of SCC presenting this type of cells need to be clarified. We report a case of a well-differentiated oral cavity SCC presenting MGCs that was analyzed by immunohistochemistry to establish the origin of these cells.

Key Words: Squamous cell carcinoma, Multinucleated giant cell, Foreign body reaction

Introduction

Squamous cell carcinoma (SCC) is the most common malignant neoplasm that occurs in the oral cavity and the aerodigestive tract [1]. Most of the cases present as conventional type, but some variants have also been described, including verrucous carcinoma, basaloid SCC, spindle cell carcinoma, and undifferentiated carcinoma [1]. The conventional type is characterized by the presence of malignant squamous epithelial cell nests, keratin pearls, and individual cell dyskeratosis. These epithelial dysplasias are common histological findings in well-differentiated oral SCC.

Although uncommon, the presence of multinucleated giant cells (MGCs) in SCC has been reported in the literature. The true nature of MGCs in SCC is controversial, and some authors believe that these cells are originated by an immune reaction against the tumor [2]; however, other authors have stated that MGCs may have a neoplastic and an inflammatory nature [3,4].

According to Donath et al. [5] foreign bodies, such as keratin, are capable of inducing a chronic granulomatous inflammation. This inflammatory reaction tends to eliminate the foreign body, and when this material is keratin, in general, it is resorbed by MGCs [5]. Foreign body MGCs are derived from the fusion of mononuclear cells, macrophages, and they play a pivotal role in chronic inflammatory diseases [6,7]. The treatment of SCC may also induce MGC formation due to a foreign body reaction [8,9]. However, McLemore et al. [2] suggest that MGCs may have a neoplastic nature, primarily when the tumor is associated with the human immunodeficiency virus (HIV).

The presence of MGCs in oral cavity SCC is a rare event and is not well described in the literature. Presence of these cells is more common in skin SCC [2-4,8-13]; however, the clinical relevance of this finding is not completely understood. The aim of this article is to present a rare case of a well-differentiated SCC of the oral cavity presenting MGCs analyzed by immunohistochemistry.

Case Report

An 86-year-old woman was referred to a maxillofacial surgeon due to a mass in her mouth floor. Clinical examination revealed a 5 cm tumor affecting the right alveolar ridge and the buccal sulcus with an ulcerated surface and necrotic center (*Figure 1*). According to the patient, the lesion had evolved 45 days earlier and was asymptomatic. The patient reported that she had done mouth rinse with guava leaf. An incisional biopsy was performed and the specimen was sent to the Oral Pathology Laboratory of the Federal University of Goiás, Brazil, with clinical hypothesis of SCC versus paracoccidioidomycosis.

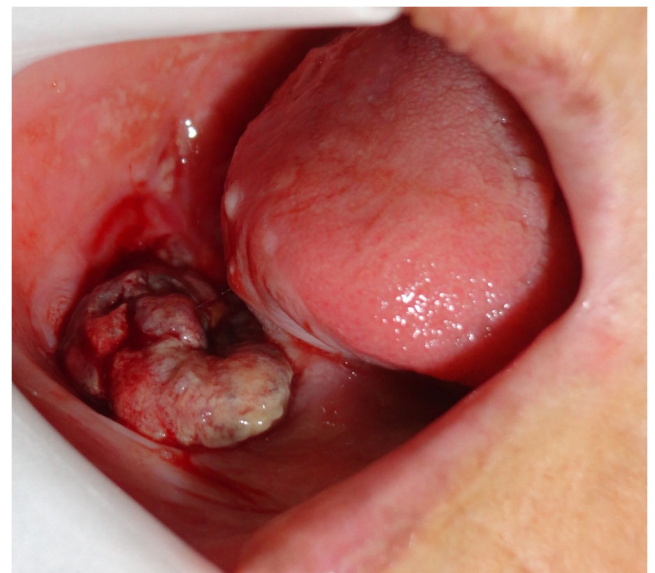


Figure 1. Clinical aspect of the lesion. Nodule of approximately 5 cm in the right side of the floor of mouth, alveolar ridge, and buccal sulcus with necrotic center and ulcerated surface.

Microscopic findings showed epithelial squamous cell nests and cords infiltrating the connective tissue with the presence of mitoses, increased nuclear/cytoplasmic ratio, epithelial microabscess, and keratin pearls; thus, the diagnosis was confirmed as a well-differentiated SCC. Interestingly, the

stroma of the lesion was rich in mononuclear inflammatory cells with the presence of MGCs (*Figure 2a*).

The MGCs were located surrounding the neoplastic cells and near the keratin pearls. The giant cells presented with small and dispersed nuclei and eosinophilic cytoplasm, and some MGCs showed the presence of vacuoles. As a differential diagnosis, the Grocott's satining was applied to

eliminate the possibility of paracoccidioidomycosis associated with SCC, and the result was negative for fungal structures (*Figure 2b*). Immunohistochemical analysis was carried out using antibody anti-CD68 and anti-pancytokeratin (AE1 and AE3 cytokeratin). The results showed that the giant cells were CD68⁺ (*Figure 2c*) and AE1/AE3⁻ (*Figure 2d*). This result suggests that giant cells had an inflammatory nature.

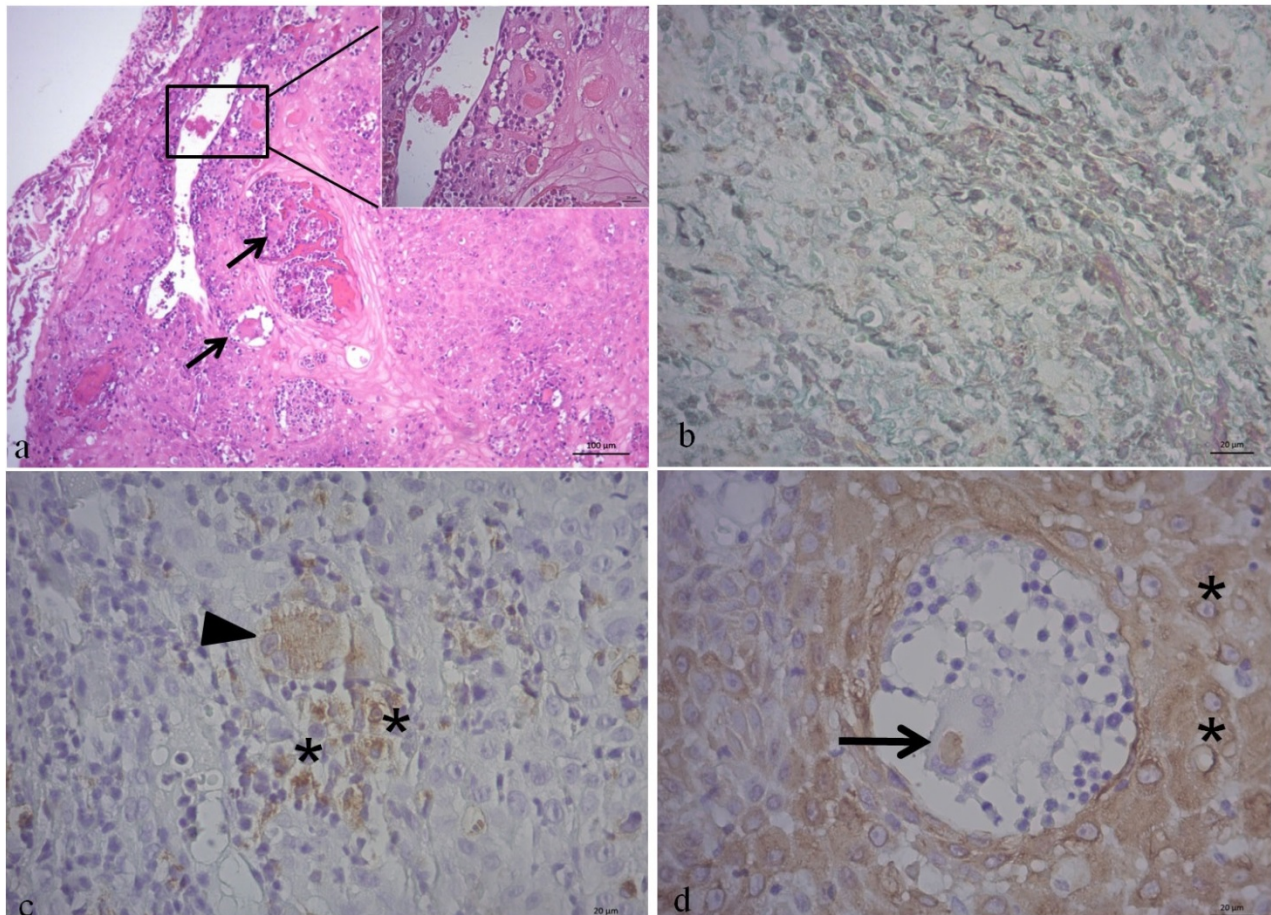


Figure 2. (a) Histological aspect of the lesion showing squamous neoplastic cells and the presence of multinucleated giant cells (black arrow), hematoxylin, and eosin (400 \times), (b) Grocott's staining negative for fungal structures, Grocott Gomori (400 \times), (c) Multinucleated giant cell (arrow head) and macrophages (asterisk) CD68⁺ in the stroma of the lesion, (d) Neoplastic cells AE1/AE3⁺ (asterisk) and a multinucleated giant cell AE1/AE3⁻ in the center of a microabscess showing a vacuole with a substance AE1/AE3⁺, suggesting keratin (black arrow).

Discussion

This case report showed the presence of MGCs in a well-differentiated oral SCC. Although the reason for this is not clear, several studies have been reported in the literature about this finding in this type of neoplastic lesion; however, this event is rare in the oral cavity (*Table 1*) [2,4,9-13]. Furthermore, the true nature of MGCs in SCC is controversial. Some authors believe that these cells are originated by an immune reaction against the tumor cells [3], while others have reported that MGCs may be of neoplastic or inflammatory origin [2,4].

In a study that investigated head and neck SCC in two groups of patients, one with HIV-positive patients and the other group untyped or HIV negative, MGCs were found in the tumoral parenchyma. The authors observed that the giant cells were more prevalent in HIV⁺ patients and that they had

various morphological features and some of them were found in the superficial layers of the epithelial tissue and underwent dyskeratosis [2]. In our case, the MGCs were restricted to the tumoral stroma and were not observed in the tumoral parenchyma.

In an experimental study using mice, applying boron neutron capture therapy, the formation of epithelial MGCs was observed in cases in which the p53 gene was mutated. The authors suggested that this type of treatment may cause mitotic catastrophes that are capable of originating MGCs of neoplastic nature in the tumoral parenchyma [8].

Westra et al. [12] studied regional metastatic SCC in the neck and showed that after treatment with chemotherapy and/or radiotherapy, a foreign body reaction to keratin with MGC occurs, suggesting that this reaction may represent a histological regression of the metastatic SCC. Moore et al. [9] also reported a case of cutaneous SCC that presented with a

foreign body reaction after irradiation. These findings suggest that the treatment may cause changes in the lesion that evoke a reaction with MGC formation.

Table 1. Case reports and studies on the multinucleated giant cell component in squamous cell carcinoma

Author	Malignancy	Location	MGC component
Moore et al. [9]	Well-differentiated SCC after radiotherapy	Right cheek	Reactive
Westra et al. [12]	SCC after chemotherapy and/or radiotherapy (including in situ poor and moderately differentiated)	Tonsil, larynx, base of tongue, pyriform sinus, and occult	Reactive
Emanuel, Shim, and Phelps [11]	Poorly differentiated SCC	Cutaneous lower lip	Uncertain (reactive?)
Woof et al. [3]	Moderately and undifferentiated SCC	Mid back; right cheek	Reactive
Beer [4]	Poorly differentiated SCC	Nose and scalp	Uncertain (reactive or neoplastic)
McLemore et al. [2]	35 typical SCCs, 4 basaloid SCCs, and 1 verrucous SCC from patients with HIV	Larynx (26 cases), Oropharynx (9 cases), oral cavity (4 cases), and nasal cavity (1 case)	Neoplastic
Patil, Rao and Ganavi [10]	Well-differentiated SCC	Oral (specific location not informed)	Reactive
Chung et al. [13]	Poorly differentiated SCC and carcinosarcoma	Skin of jawline, arm, and calf	Reactive
Present case	Well-differentiated	Oral cavity (alveolar ridge)	Reactive

Foreign bodies present in the connective tissue, such as keratin, are capable of inducing chronic inflammation as a granulomatous reaction with MGC formation. MGCs are derived from the fusion of macrophages or monocytes, and their primary function is to degrade and reabsorb a substrate [6]. In well-differentiated SCC, the neoplastic cells may present with an excessive keratin production and evoke an inflammatory response with a foreign body reaction.

In a case reported of a poorly differentiated SCC that affected the cutaneous lower lip showing association with MGCs, the giant cells were described as morphologically indistinguishable from osteoclasts but with some characteristics that favored a reactive inflammatory nature. However, the authors believe that the MGCs did not represent a foreign body reaction, since they observed a lack of foreign body or keratin and little inflammatory infiltrate. They suggested that the lesion could represent an association between SCC and dermatofibroma [11].

The SCC presenting with MGCs may also interfere with the differential diagnosis [3,4]. Beer [4] describes two cases of SCC that was previously diagnosed as atypical fibroxanthoma; however, after careful review and immunostaining that included melanocytic and epithelial markers, the cases were diagnosed as poorly differentiated SCC with osteoclast-like giant cells. Woof et al. [3] suggest that an immunohistochemical panel is important to differentiate lesions with MGCs from lesions with sarcomatous differentiation. Chung et al. [13] suggest using immunohistochemical staining for keratin or p⁶³ to prevent misdiagnosis. In the present case, the differential diagnosis was believed to be paracoccidioidomycosis due to the chronic inflammatory pattern of the lesion. To establish the final diagnosis, a panel immunohistochemistry was carried out using AE1/AE3 (pan-keratin) and CD68 (histiocytes) and histochemical technique (Grocott's staining) to investigate fungal infection. The results showed MGCs positive for CD68

and epithelial cells positive for AE1/AE3. Grocott's staining test was negative for the whole specimen.

Interestingly, Patil et al. [10] reported a well-differentiated oral SCC with MGCs in close association with keratin pearls, keratin debris, or keratinizing tumor cells with a dense chronic inflammatory infiltrate. In their case also, the immunohistochemical analysis showed that MGCs were CD68⁺ as in our case, and the authors considered the cells as foreign body type [9]. Although, the presence of MGCs in oral SCC tumoral stroma is not well documented in the literature, based on microscopic findings associated with the clinical features of the lesion and the immune status of the patient, the MGCs present in tumoral stroma of our case were classified as inflammatory foreign body-like type.

This case study reports an uncommon finding of MGCs in the tumoral stroma in an untreated well-differentiated SCC. Although rare, when this condition occurs, a differential diagnosis is mandatory with granulomatous inflammatory diseases such as paracoccidioidomycosis. The Grocott's staining method was essential for making the correct diagnosis associated with the immunohistochemistry technique. This event is indicative of the participation of the tumoral microenvironment in the carcinogenesis process. Research on the role played by the MGC in both stroma and tumoral parenchyma and its relation with clinical prognosis needs to be continued.

References

1. Stelow EB, Mills SE. Squamous cell carcinoma variants of the upper aerodigestive tract. *American Journal of Clinical Pathology*. 2005; **124**: S96-S109.
2. McLemore MS, Haigentz M, Smith RV, Nuovo GJ, Alos L, et al. Head and neck squamous cell carcinoma in HIV-Positive patients: A preliminary investigation of viral associations. *Head and Neck Pathology*. 2010; **4**: 97-105.

3. Wooff J, Werner D, Murphy J, Walsh N. Osteoclastic-like giant cell reaction: Associated with cutaneous squamous cell carcinoma: A report of 2 cases and review of the literature. *The American Journal of Dermatopathology*. 2009; **31**: 282-287.

4. Beer TW. Squamous cell carcinoma with osteoclast-like giant cells: 2 cases misdiagnosed as atypical fibroxanthoma. *The American Journal of Dermatopathology*. 2010; **32**: 414-415.

5. Donath K, Laab M, Günzl HJ. The histopathology of different foreign-body reactions in oral soft tissue and bone tissue. *Virchows Archiv. A, Pathology. Pathologische Anatomie*. 1992; **420**: 131-137.

6. Bordbeck WG, Anderson JM. Giant cell formation and function. *Current Opinion in Hematology*. 2009; **16**: 53-57.

7. Vignery A. Macrophage fusion: the making of osteoclasts and giant cells. *The Journal of Experimental Medicine*. 2005; **202**: 337-340.

8. Fujita Y, Yamamoto N, Kato I, Iwai S, Ono K, et al. Induction of multinucleation in oral squamous cell carcinoma tissue with mutated p53 surviving boron neutron capture therapy. *International Journal of Radiation Biology*. 2011; **87**: 293-301.

9. Moore T, Moore AY, Langer M, Wagner RF. Tumor remnants within giant cells following irradiation of cutaneous squamous cell carcinoma. *Dermatologic Surgery*. 1998; **24**: 1094-1096.

10. Patil S, Rao RS, Ganavi BS. A foreigner in squamous cell carcinoma! *Journal of International Oral Health*. 2013; **5**: 147-150.

11. Emanuel PO, Shim H, Phelps RG. Poorly differentiated squamous cell carcinoma with osteoclastic giant-cell-like proliferation. *Journal of Cutaneous Pathology*. 2007; **34**: 930-933.

12. Westra WH, Forastiere AA, Eisele DW, Lee DJ. Squamous cell granulomas of the neck: histologic regression of metastatic squamous cell carcinoma following chemotherapy and/or radiotherapy. *Head & Neck*. 1998; **20**: 515-521.

13. Chung HJ, Wolpowitz D, Scott G, Gilmore E, Bhawan J. Squamous cell carcinoma with osteoclast-like giant cells: a morphologically heterogeneous group including carcinosarcoma and squamous cell carcinoma with stromal changes. *Journal of Cutaneous Pathology*. 2016; **43**: 148-157.