J. Oral Diag. 2017; 02:e20170041

ORIGINAL ARTICLE

Melanoma of the oral mucosa: report of an aggressive case and review of the literature

Isabella Jardelino Dias [1]
Iroildo Jacinto Ferreira Filho [1]
Jozinete Vieira Pereira [1]
Bárbara Vanessa de Brito Monteiro [1]
Cassiano Francisco Weege Nonaka [1]
Polliana Muniz Alves [1]
Daliana Queiroga de Castro Gomes [1]

Abstract:

Introduction: Melanoma is an aggressive malignant neoplasm of uncertain etiology. Although the third most common skin cancer, melanoma is rare in the oral cavity, accounting for less than 1% of all melanomas and for 0.5% of all malignant oral tumors. Objective: This study reports a case of melanoma diagnosed and followed up by the dentistry team of the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil. Case report: A 69-year-old dark-skinned male patient was referred to the stomatology service of the hospital reporting pain and bleeding in the upper alveolar ridge, as well as the presence of a "lump" at the same site. Intraoral physical examination revealed a purple nodule of soft consistency in the anterior maxilla, which measured 2.0 cm in diameter and exhibited superficial ulcerations. An incisional biopsy was performed and histopathological analysis revealed intense proliferation of atypical melanocytes characterized by variable degrees of pleomorphism and nuclear hyperchromatism. The diagnosis was melanoma of the oral mucosa. The patient underwent surgical resection consisting of complete removal of the tumor with wide safety margins, chemotherapy, and adjuvant radiotherapy. The patient continues under follow-up and showed no recurrence of the lesion one year after surgery. Conclusion: Melanoma of the oral mucosa exhibits an aggressive behavior and rapid growth, as observed in the present case. Knowledge of the clinical and etiopathogenic features is important for the early diagnosis of the disease in order to improve patient survival.

Keywords: Melanoma; Mouth Neoplasms; Pigmentation; Oral Health.

[1] State University of Paraíba;Department Odontology - Campina Grande - Paraíba - Brasil.

Correspondence to:
Isabella Jardelino Dias.
E-mail: isabella_jdias@hotmail.com

Article received on March 7, 2017.
Article accepted on May 18, 2017.

DOI: 10.5935/2525-5711.20170041

CC BY

INTRODUCTION

Pigmented lesions of the oral cavity represent alterations in the natural color of the mucosa that depend on the degree of keratinization, melanogenic activity, number of melanocytes, and/or vascularization in the area. These lesions can manifest in different circumstances, either as physiological alterations such as racial pigmentation or as systemic events such as Addison's disease. Moreover, these manifestations can also be found in rare oral neoplasms such as melanomas[1,2].

Melanoma is a malignant neoplasm of uncertain etiology that arises from the atypical proliferation of melanocytes. The latter are cells derived from the neuroectoderm that produce the pigment melanin and reside in the basal layer of the epithelium[3]. Although the third most common skin cancer, melanoma is extremely rare in the oral cavity, accounting for less than 1% of all melanomas and for about 0.5% of all malignant oral tumors[2,4].

Clinically, melanoma is characterized by dark pigmented lesions with a brown-purple to black color and irregular and asymmetric borders. In rare cases, the lesions have a normal mucosa-like color, a fact that makes their diagnosis difficult. These lesions are called amelanotic melanomas. Melanomas first appear with a macular surface that extends laterally and subsequently form a nodule that exhibits aggressive vertical growth. An association with pain, bleeding and bone destruction has been described, especially when accompanied by tissue ulceration. However, melanomas are commonly asymptomatic at the time of diagnosis[5,6].

Melanoma of the oral cavity mainly affects the hard palate, but can also be found at other sites of the oral mucosa such as the soft palate, gingiva and alveolar ridge. Less common sites are the tongue and floor of the mouth. This cancer affects men and women at a proportion of 2:1 and more commonly occurs at older ages (mean of 60 years)[1,7].

The epidemiological and clinical characteristics cited are important signs so that histopathological examination can subsequently define the correct diagnosis of the disease. Important histological features of melanomas are pleomorphic and hyperchromatic cells with intense mitotic activity forming sheets at the junction between the epithelium and underlying connective tissue, or deeply invading the latter tissue. Atypical melanocytes also exhibit important nuclear alterations such as large hyperchromatic, sometimes multiple, nuclei with prominent nucleoli[8].

Despite the low frequency of this cancer in the oral cavity, it is important that dentists are able to identify these alterations, differentiating this cancer from lesions such as amalgam tattoo which is caused by the entry of restorative material into the mucosa; physiologic melanin pigmentation which is caused by endocrine factors that increase the production and deposition of melanin, and nevi which are small dark pigmented maculae that can occur in any area of the oral mucosa. Thus, careful evaluation and adequate consideration are necessary for a correct diagnosis[9].

The currently best method for the treatment of melanoma is radical surgical excision consisting of the removal of the tumor with wide margins, combined with radiotherapy and/or chemotherapy as adjuvant treatment. The prognosis is guarded and is directly related to the size and depth of the tumor, presence or absence of vascular invasion, necrosis, population of polymorphic neoplastic cells, lymph node involvement, and metastasis[10,11].

In view of the rarity and generally obscure prognosis of oral mucosal melanoma, the objective of this study was to report a case of extensive melanoma diagnosed and followed up by the dentistry team of the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil.

CASE REPORT

A 69-year-old dark-skinned male patient was referred to the stomatology team of the Napoleão Laureano Hospital, João Pessoa, Paraíba, Brazil, for assessment of an extensive lesion in the oral cavity. Wearing an upper denture, the patient complained of pain and bleeding in the upper alveolar ridge, which provided support to the denture, as well as of the presence of a "lump" at the same site.

During anamnesis, the patient reported to have been an active smoker for 50 years, consuming 20 cigarettes per day during this period, but had quit smoking 4 years prior to the occurrence of the lesion. He also reported no family history of malignant neoplasms and no history of alcoholism, systemic diseases or childhood diseases.

No palpable lymph nodes or any other alterations were detected upon extraoral physical examination. Initial intraoral examination showed an exophytic, sessile, variably colored nodule of soft consistency in the anterior maxilla, which measured 2.0 cm in diameter and exhibited superficial ulcerations. In addition, black and brown spots extending bilaterally to the upper lip and ridge of the jaw were observed (Fig. 1).

Figure 1. Intraoral clinical aspect of the lesion.

Based on these features, the diagnostic hypothesis was melanoma of the oral mucosa. A panoramic radiograph was requested for the evaluation of bone involvement. Preoperative blood tests and an incisional biopsy were obtained.

Radiography did not show extension of the lesion into bone (Fig. 2) and the region of the anterosuperior ridge had a normal pattern. The biopsy specimen was sent for histopathological analysis, which revealed proliferation of spindle-shaped, sometimes epithelioid, atypical melanocytes throughout the connective tissue.

Figure 2. Panoramic radiograph showing no evidence of bone involvement.

These cells were arranged in bundles or nests and exhibited variable degrees of pleomorphism and cellular hyperchromatism (Fig. 3). Many of these neoplastic cells contained brown cytoplasmic granules compatible with melanin. The lesion was lined with parakeratinized stratified squamous epithelium exhibiting atypical and pleomorphic melanocytes in the basal and suprabasal layers. Some of these melanocytes contained brown cytoplasmic pigments compatible with melanin. An area of ulceration with extravasation of erythrocytes was also observed. The combined analysis of these findings led to the diagnosis of melanoma of the oral mucosa.

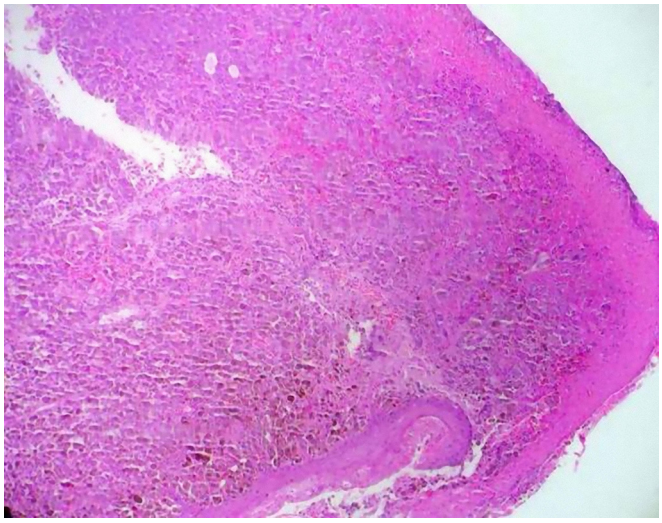

Figure 3. Photomicrograph showing proliferation of atypical, epithelioid to spindle-shaped melanocytes exhibiting variable degrees of pleomorphism and hyperchromatism (HE, 40X).

The patient was referred to the head and neck surgery sector of the Napoleão Laureano Hospital, where he underwent mucosectomy with partial maxillectomy and reconstruction of the area with a nasolabial flap. A few days after surgery, the patient was referred to a clinical oncologist who opted for chemotherapy as adjuvant treatment.

The treatment regimen consisted of six cycles of temozolomide (Temodal®) every 28 days, with each cycle lasting five days. Three capsules of 100 mg and one capsule of 20 mg of temozolomide were administered after fasting, totaling a daily dose of 320 mg. In addition, 1 mg/ml cisplatin was prescribed for four consecutive days.

Good healing of the graft and of the area of bone exposure on the left side of the maxillary alveolar ridge was observed 30 days after surgery. In addition, hair growth was noted due to the origin of the graft (Fig. 4).

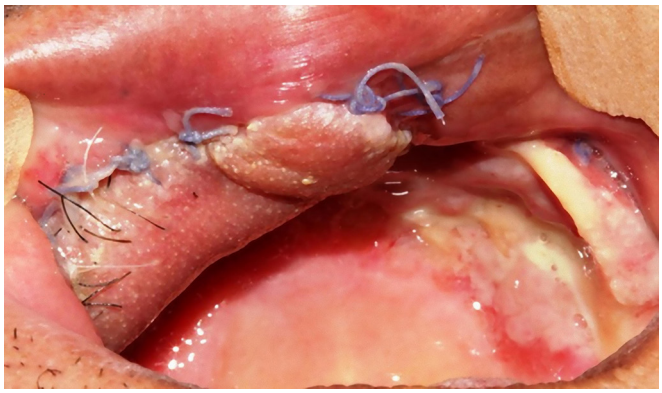

Figure 4. Clinical aspect 30 days after excision of the lesion.

During chemotherapy, specifically after the fourth cycle of temozolomide, the patient developed nephropathy and the medication was discontinued. The patient was then referred for assessment by a radiotherapist who requested a computed tomography scan, which revealed a lytic lesion in the right upper alveolar ridge.

In view of this presentation, the radiotherapist referred the patient for head and neck surgery. A new biopsy was obtained from the area and the histopathological analysis showed an oral mucosa with acanthosis and papillomatosis and cancer-free bone and fibroadipose connective tissue. After the histopathological result, the patient was submitted to adjuvant radiotherapy consisting of 10 irradiations with a dose of 30 Gy. Radiotherapy was delivered without interruption due to toxicity, with the patient only reporting odynophagia at the end of treatment.

The patient showed no recurrence of the disease one year after surgical resection and was asked to periodically come to the hospital for evaluation of the health conditions related to the lesion removed. The patient is undergoing continuous follow-up by the medical and dental team to ensure the early diagnosis of any sign of recurrence or metastasis of melanoma.

DISCUSSION

The present study describes a case of melanoma of the oral mucosa, a rare and aggressive disease that arises from the malignant transformation of cells found in the epithelium, called melanocytes. The prognosis of melanoma is generally unfavorable. Melanoma is a malignant neoplasm with a tendency for metastasis because of the easy penetration of vascular and lymphatic structures and, consequently, with greater lethality than other tumors of the oral cavity[12].

Melanoma generally appears as dark pigmented lesions and may have an unresolved differential diagnosis with other pigmented lesions. Thus, the ABCD system of evaluation was developed to classify these entities based on their asymmetry (A), border irregularity (B), color (C), and diameter (D)[9]. According to these parameters, a melanoma would be characterized as an asymmetric lesion with irregular borders, color variation of brown, black, white, red or blue, and a diameter greater than 6.0 mm[11]. The lesion of the present patient met all of these specifications, except for its greater dimension (diameter of 2.0 cm) which can be attributed to the advanced stage of the cancer. Importantly, all clinically suspicious lesions should be biopsied to establish the definitive diagnosis.

Melanocytes are found in the basal layer of the epithelium. Under normal conditions, these cells are responsible for the production of melanin, a physiological pigment present in the epidermis[13]. In melanomas, melanocytes are atypical, exhibiting variable degrees of pleomorphism and nuclear hyperchromatism and proliferating in a disordered manner through the epithelium into the underlying connective tissue[8]. These features are similar to those obtained in the histopathological analysis of the present case, supporting the diagnosis of melanoma.

Immunohistochemistry is a tool used in situations in which the histopathological report is not conclusively diagnostic. Specific tumor markers such as S-100, Melan-A, HMB-45 and Ki-67 are used for the differential diagnosis of melanoma. However, the clinical and histopathological evidence of the present case rules out any possibility of doubtful interpretation of the diagnosis, differing clearly from the pigmented lesions found in Addison's disease, Peutz-Jeghers syndrome, Kaposi's sarcoma, amalgam tattoo, nevus, melanotic pigmentation, and melanoacanthoma[14].

The etiopathogenesis of melanoma remains unknown. The proliferation of neoplastic cells is not related to any causal factor and the lesions tend to arise from melanocytes in apparently normal mucosa or from benign melanocytic lesions[6,15]. Rani *et al.*[5] and Misir *et al.*[16] highlight that, in the past, melanoma was associated with habits such as smoking, alcohol consumption and exposure to ultraviolet radiation. These facts would explain the occurrence of melanoma in the case reported here since the patient had been exposed to the deleterious effects of smoking for many years. However, there is currently no scientific evidence that would solidly validate this theory.

According to Lourenço *et al.*[15] and Sortino-Rachou *et al.*[17], melanoma mainly affects adults, with a peak incidence in the fourth decade of life and extending until the seventh decade. The present patient was within the age group described, with 69 years old. Regarding ethnicity, Smith *et al.*[8] and Pandey *et al.*[18] indicate that 80% of cases of oral mucosal melanoma are whites, especially of Asian origin. However, it is assumed that studies like those of the authors were conducted in countries without the racial miscegenation characteristics of the Brazilian population, which is formed by individuals with multiple ethnic characteristics, such as dark-skinned individuals that possess white, black and indigenous traits.

In the present case, the lesion arose in the mucosa of the upper alveolar ridge. According to Mohan *et al.*[19] and Kumar *et al.*[20], this is a common site for the occurrence of dark pigmented lesions, with 80% of oral melanomas occurring in the maxilla. Rubio-Correa *et al.*[21] report the base of the tongue also to be susceptible to development of the disease.

Melanoma of the oral mucosa is generally painless, a fact that leads to a delay in seeking dental care until common symptoms occur such as denture problems, ulcers, bleeding, nodules, pain, tooth mobility, and paresthesia[22]. Corroborating these data, the clinical presentation of the case described here was initially asymptomatic and the patient sought a specialized service only after the lesion had grown significantly and the swelling interfered with the use of the denture. Thus, because of the asymptomatic behavior of melanomas in their early phases, most patients are diagnosed in an advanced stage of the disease[15,23-25].

The present patient was submitted to surgical resection consisting of complete removal of the tumor with wide safety margins, in agreement with the study of Lazarev *et al.*[10]. In a systematic literature review, these authors found that primary melanomas are well controlled by the surgical methods cited, if properly executed.

Chemotherapy and radiotherapy are effective adjuvant therapies in cancer treatment and were therefore included in the treatment plan reported here. The objective of radiotherapy is to promote better regional control and prevent recurrence of the disease. Chemotherapy is used as a palliative measure in cases of extensive lesions, surgical impossibility or refusal of the patient to undergo invasive procedures[18,26,27]. Adjuvant therapies were indicated in the present case because of the extensive, and probably advanced, lesion, the aggressive vertical growth detected in the histopathological exam, and the considerable size observed by clinical examination.

In the present study, chemotherapy consisted of the combination of two substances: temozolomide and cisplatin. Temozolomide is an orally administered drug that has been introduced by the Chinese Society of Clinical Oncology as an effective drug for the treatment of melanomas. The potent effect of the drug is due to its ability to prevent the formation of brain metastases, which are observed in more than 50% of cases of metastatic melanoma.

In a clinical study involving a large sample[28], temozolomide provided the best clinical outcomes when compared to treatments with traditional drugs. In that study, the recommended daily dose was 250 mg for 5 consecutive days, repeating the cycle after 4 weeks. A higher dose, 320 mg/day, was used in the present case because of the extent and aggressiveness of the lesion.

Cisplatin, a platinum-based antitumor medication, shows high effectiveness in the treatment of patients with melanoma. Despite these positive results, the effects exerted by this drug are short-lived and are associated with high toxicity. Thus, cisplatin is indicated for combination cancer therapy with other drugs such as temozolomide so that cisplatin would only be prescribed for a few days, potentiating the effect of chemotherapy and minimizing its undesired effects[29].

Although melanoma is a rare malignant neoplasm in the oral mucosa, it exhibits a very aggressive behavior and, consequently, an unfavorable prognosis[3,5,30]. These facts highlight the importance of an early diagnosis and intervention for any pigmented lesion arising in the oral mucosa since lesions that are detected early and removed before the development of metastases will have a better prognosis and are associated with higher survival rates.

CONCLUSIONS

Melanoma of the oral mucosa is a rare malignant neoplasm of obscure diagnosis that is usually asymptomatic. This generally results in the identification of the disease at advanced stages, as evidenced in the present case, whose biological behavior exhibited aggressiveness and rapid growth, clinically demonstrated by the extent of the lesion as well as the histopathological appearance of atypical melanocytes with vertical expansion. The knowledge of these characteristics by dentist is extremely relevant for the identification of melanoma, even as its differentiation from other oral pigmented lesions, thus making it possible to cure the patient by early treatment of the disease.

REFERENCES

1. Vasconcelos RG, Moura IS, Medeiros LKS, Melo DS, Vasconcelos MG. Main blackened lesions of the oral cavity. Rev Cubana Estomatol. 2014;51:195-205.
2. Martinelli-Kläy CP, Laporte ML, Martinelli CR, Martinelli C, Lombardi T. Oral Malignant Melanoma Initially Misdiagnosed as a Racial Pigmentation: A Case Report. Dermatopathology (Basel). 2016;3:1-7.
3. Mosalleum E, Afrogheh A, Dreyer WP, Schneider JW. Oral medicine case book 61: Oral malignant melanoma. SADJ. 2014;69:276-8.
4. Garzino-Demo P, Fasolis M, Maggiore GM, Pagano M, Berrone S. Oral mucosal melanoma: a series of case reports. J Craniomaxillofac Surg. 2004;32:251-7.

5. Rani GS, Kumar TV, Kolasani B, Begum MR, Priya Srinivasan A. Primary malignant melanoma of maxilla: report of a case with discussion. Case Rep Dent. 2014;4:624306.
6. Francisco AL, Furlan MV, Peresi PM, Nishimoto IN, Lourenço SV, Pinto CA, *et al.* Head and neck mucosal melanoma: clinicopathological analysis of 51 cases treated in a single cancer centre and review of the literature. Int J Oral Maxillofac Surg. 2016;45:135-40.
7. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2002;55:74-108.
8. Smith MH, Bhattacharyya I, Cohen DM, Islam NM, Fitzpatrick SG, Montague LJ, *et al.* Melanoma of the Oral Cavity: an Analysis of 46 New Cases with Emphasis on Clinical and Histopathologic Characteristics. Head Neck Pathol. 2016;10:298-305.
9. Vikey AK, Vikey D. Primary malignant melanoma, of head and neck: a comprehensive review of literature. Oral Oncol. 2012;48:399-403.
10. Lazarev S, Gupta V, Hu K, Harrison LB, Bakst R. Mucosa melanoma of the head and neck: a systematic review of the literature. Int J Radiat Oncol Biol Phys. 2014;90:1108-18.
11. Chatzistefanou I, Kolokythas A, Vahtsevanos K, Antoniades K. Primary mucosal melanoma of the oral cavity: current therapy and future directions. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:17-27.
12. Lamichhane NS, An J, Liu Q, Zhang W. Primary malignant mucosal melanoma of the upper lip: a case report and review of the literature. BMC Res Notes. 2015;8:499.
13. Tas F, Keskin S. Mucosal melanoma in the head and neck region: different clinical features and same to cutaneous melanoma. ISRN Dermatol. 2013;2013:586915.
14. Ahmadi-Motamayel F, Falsafi P, Baghaei F. Report of a rare and aggressive case of oral malignant melanoma. Oral Maxillofac Surg. 2013;17:47-51.
15. Lourenço SV, Fernandes JD, Hsieh R, Coutinho-Camillo CM, Bologna S, Sanqueza M, *et al.* Head and neck mucosal melanoma: a review. Am J Dermatopathol. 2014;36:578-87.
16. Misir AF, Durmuslar MC, Zerener T, Gün BD. Primary malignant melanoma. Saudi Med J. 2016;37:446-9.
17. Sortino-Rachou AM, Cancela Mde C, Voti L, Curado MP. Primary oral melanoma: population-based incidence. Oral Oncol. 2009;45:254-8.
18. Pandey M, Mathew A, Iype EM, Sebastian P, Abraham EK, Nair KM. Primary malignant melanoma of the head and neck region: pooled analysis of 60 published cases from India and review of literature. Eur J Cancer Prev. 2012;11:3-10.
19. Mohan M, Sukhadia VY, Pai D, Bhat S. Oral malignant melanoma: systematic review of literature and report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116:e247-54.
20. Kumar V, Vishnoi JR, Kori CG, Gupta S, Misra S, Akhtar N. Primary malignant melanoma of oral cavity: A tertiary care center experience. Natl J Maxillofac Surg. 2015;6:167-71.
21. Rubio-Correa I, Solo de Zaldívar DM, Sánchez MM, Laza LR, González Ballester D, Monje-Gil F. Mucosa melanoma in an extremely rare location: base of the tongue. A case presentation and literature review. Rev Esp Cir Oral Maxilofac. 2015;37:99-102.
22. Padhye A, D´souza J. Oral malignant melanoma: A silent killer? J Indian Soc Periodontol. 2011;15:425-8.
23. Femiano F, Lanza A, Buonaiuto C, Gombos F, Di Spirito F, Cirillo N. Oral malignant melanoma: a review of the literature. J Oral Pathol Med. 2008; 37:383-8.
24. Pour MAH, Rad M, Zarei MR, Chamani G. Malignant Mucosal Melanoma of the Head and Neck Diagnosed in an Iranian Population over an 11-Year Period. Am J Appl Sci. 2009;6:1467-72.
25. Guevara-Canales J, Gutiérrez-Morales MM, Sacsaquispe-Contreras SJ, Sanchez-Lihón J, Morales-Vadillo R. Malignant melanoma of the oral cavity. Review of the literature and experience in a Peruvian population. Med Oral Patol Oral Cir Bucal. 2012:17:e206-11.
26. Marta GN, Bergamasco VD, Rodrigues ML, Cerávolo FP, Landman G, Kowalski LP, *et al.* Melanoma de mucosa oral. Rev Bras Cancerol. 2007;53:35-9.
27. Wu AJ, Gomes J, Zhung JE, Chan K, Gomez DR, Wolden SL, *et al.* Radiotherapy after surgical resection for head and neck mucosal melanoma. Am J Clin Oncol. 2010;33:281-5.
28. Guo J, Qin S, Liang J, Lin T, Si L, Chen X, *et al.*; Chinese Society of Clinical Oncology (CSCO) Melanoma Panel. Chinese Guidelines on the Diagnosis and Treatment of Melanoma. Ann Transl Med. 2015;3:322.
29. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, *et al.* Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18:158-66.
30. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol. 2012;5:739-53.