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Metastatic oral melanoma: radiotherapy and nivolumab treatment

Melanoma oral metastático: tratamento com radioterapia e nivolumabe

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ABSTRACT: INTRODUCTION: Oral Mucosa Melanoma (MMO) is a rare malignant neoplasm that accounts for about 0.5% of all oral tumors. This melanoma is associated with atypical proliferation of melanocytes present in the mucosal epithelium. The treatment can be performed by surgical resection, with chemotherapy and radiotherapy as adjunct treatment. In cases with metastatic lymph nodes, adjuvant treatment with immunotherapy may be used. CASE REPORT: An 83-year-old male patient had as main complaint a dark tumor in the gingiva, hard palate and right maxillary sinus, with cervical and mediastinal lymph nodes and pulmonary metastases. In 2015, he started treatment with DTIC and obtained partial response. After one year, he started treatment with Imatinib, obtained partial response and then disease progression. In 2016, he started treatment with Nivolumab and local radiotherapy with IMRT. He had complete local remission and partial systemic remission. Moreover, the treatment had as immune-mediated side effects adrenal insufficiency, hypothyroidism, diabetes mellitus and vitiligo on face and left flank. Our report aims to present a case of oral mucosal melanoma in the gingiva, palate and maxillary sinus with systemic metastases, treated with Nivolumab and radiotherapy, compare it with other reports in the literature and highlight the complications of immunotherapy.

Keywords: Melanoma; Immunotherapy; Nivolumab; Radiotherapy.

RESUMO: INTRODUÇÃO: O Melanoma de Mucosa Oral (MMO) é uma neoplasia maligna rara, corresponde a cerca de 0,5% de todos os tumores orais. Este melanoma ocorre devido a proliferação atípica de melanócitos presentes no epitélio das mucosas do organismo. O tratamento é realizado por ressecção cirúrgica, quimioterapia e radioterapia como tratamento adjuvante. Nos casos com linfonodos metastáticos pode-se usar o tratamento adjuvante com imunoterapia. RELATO DE CASO: Paciente 83 anos, sexo masculino, teve como queixa principal tumoração de cor escura em gengiva, palato duro e seio maxilar direito, com linfonodos metastáticos cervicais e mediastinais e metástases pulmonares. Em 2015, iniciou tratamento com DTIC com resposta parcial e após um ano, iniciou a terapêutica com Imatinibe com resposta parcial e depois progressão da doença. Em 2016, iniciou tratamento com Nivolumabe e radioterapia local com IMRT. Apresentou remissão completa local e parcial sistêmica. Também apresentou como efeitos colaterais imunomediados insuficiência suprarrenal, hipotireoidismo, diabetes melitus e vitiligo em face e flanco esquerdo. Nosso relato tem como objetivo apresentar um caso de melanoma de mucosa oral na região da gengiva, palato e seio maxilar com metástases sistêmicas, tratado com Nivolumabe e radioterapia, e com isso comparar com outros relatos existentes na literatura e ressaltar as complicações da imunoterapia.

Palavras-chave: Melanoma; Imunoterapia; Nivolumabe; Radioterapia.

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INTRODUCTION

Oral Mucosal Melanoma (OMM) is a rare malignant neoplasm that is distinct from other melanomas that appear on the skin. It represents 0.2% to 8% of all melanomas and 0.5% of all oral tumors[1]. As melanocytes are abundant in the skin, melanoma can be found in small numbers in the mucosa of the digestive, respiratory and genitourinary systems, as well as in the eye. Melanoma occurs due to the atypical proliferation of melanocytes in the mucosa of these organs and is characterized by the aggressive vertical growth of these cells.

Of the 87,110 melanoma cases diagnosed in the United States in 2017/2018, less than 2% are in the mucosa: 31% to 55% are in the head and neck, 17% to 24% are in the anorectal area and 18% to 40% are in the vulva and vagina. While cutaneous melanoma is slightly more common in men than in women, the incidence of mucosal melanoma is 87% higher in women than in men[2,3,4].

The epidemiology of mucosal melanoma is different from cutaneous melanoma. Melanomas of the oral cavity represent almost 30% of the mucosal melanomas of the head and neck and usually affect the palate and buccal gingiva. Mucosal melanomas are usually diagnosed at advanced stages and have poor prognosis and survival. The 5-year survival rate for head and neck mucosal melanoma ranges from 17% to 35%. The prognosis, however, seems to vary according to the location: lesions in the nasal cavity have a more favorable prognosis than those of the sinuses[5,6].

An analysis of 93 patients with mucosal melanoma showed c-KIT mutations in 18.2% of melanomas, BRAF mutations in 12% and NRAS mutations in 10%. NFI appears in 20% of melanomas of the anorectal mucosa, while BRAF appears in 52% of cutaneous melanomas[7] .

The main treatment for localized oral melanoma is wide surgical resection with radiotherapy as adjuvant treatment [(5)(8)]. After surgical resection, the recommendation of adjuvant treatment is based on a phase III study conducted in China. In this study, 204 patients that underwent complete resection were randomized to receive alpha interferon or chemotherapy with cisplatin and temozolomide for 6 cycles. The study had a median follow-up of 23.7 months and disease-free survival was 16.80 months for patients on alpha interferon versus 9.57 months for patients on chemotherapy. For metastatic melanoma, treatment with targeted BRAF inhibitors (dabrafenib and trametinib), anti-PD-1 antibodies (nivolumab and pembrolizimab) and anti-CTLA-4 (ipilumumab) is currently recommended as adjuvant and palliative treatment according to the occurrence of mutations and other factors[9,10].

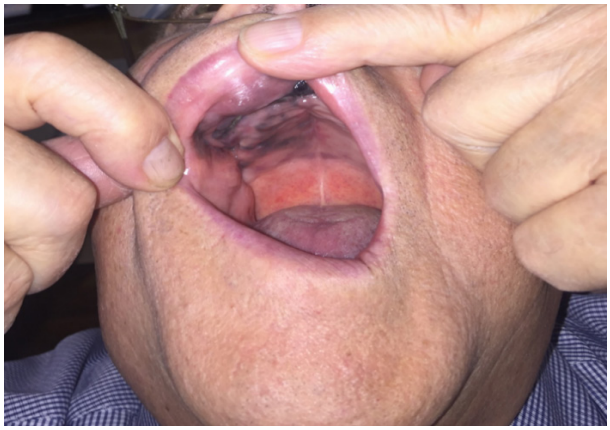
CASE REPORT

The patient is an 83-year-old Brazilian white male, retired military police officer, currently undergoing treatment at the Oncology and Chemotherapy Simões Institute (ISOQ). In 2015, the main complaint of the patient was a dark tumor on the hard palate, gingiva and right side of the maxillary sinus, in addition to bilateral level II metastatic cervical lymph nodes. He also had metastatic mediastinal lymph nodes and lung metastases shown on imaging tests and PET-CT scans. A lung biopsy confirmed a metastatic melanoma of the lung. His personal history includes diabetes treated with metformin, prostate cancer confirmed by biopsy, with Gleason score of 8 and 6, treated with agonist LHRH since 2013 and SAH and diabetes with stable PSA. Patient denies family history of melanoma.

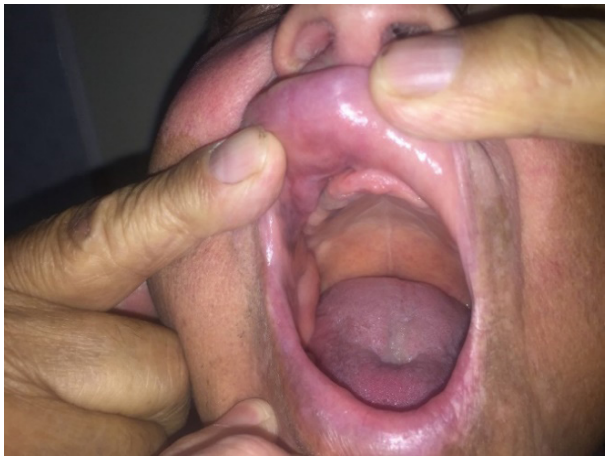
In March 2015, the patient was diagnosed with Mucosal Melanoma of the palate and gingiva with invasion of the right maxillary sinus and started treatment by the SUS in another institution. The physical examination showed a dark ulcerated exophytic tumor in the hard palate and gingiva, invading the right maxillary sinus, and bilateral level II metastatic cervical lymphadenopathy. An open lung biopsy showed metastasis of the melanoma (stage IV b). The patient started treatment with DTIC (Dacarbazine) for six cycles and obtained a partial response. At the beginning of 2016, he started treatment at the ISOQ with Imatinib (Glivec) for cKIT-Positive, BRAF-negative and normal LDH for 6 cycles and obtained partial response.

After local and systemic progression of the disease, in August 2016, the patient started treatment with Nivolumab 200 mg IV every fortnight and, after 4 cycles, he started local radiotherapy with IMRT. He obtained complete locoregional response in the following months and an important systemic response, confirmed by imaging tests and PET-CT. Brain MRI was normal.

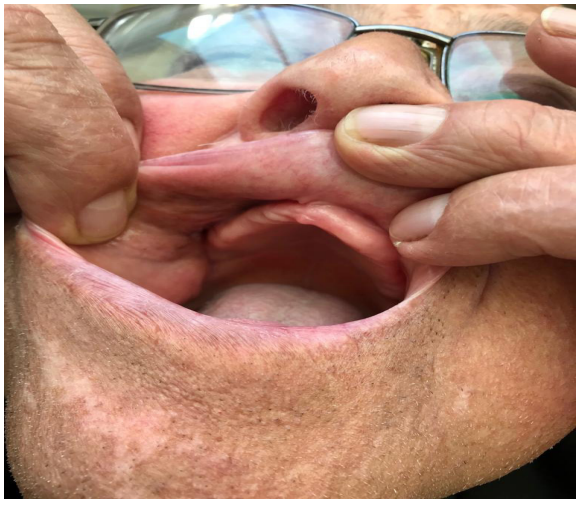
After 6 months, there were adverse immunological effects: adrenal insufficiency with a baseline cortisol level of 0.14 (nv 6.70 to 22.60), which was managed with oral Prednisone and maintained with 5 mg VO 12/12 h, and hypothyroidism with 7.17 TSH (nv - 4.6), treated with Puran T4 50 ucg/day. He also had vitiligo in the face and left flank. In 2018, his diabetes got worse and he needed insulin treatment, which is maintained until today. The patient remained in complete response for more than 3 years without progression of the disease, which was confirmed by a PET-CT and brain MRI.



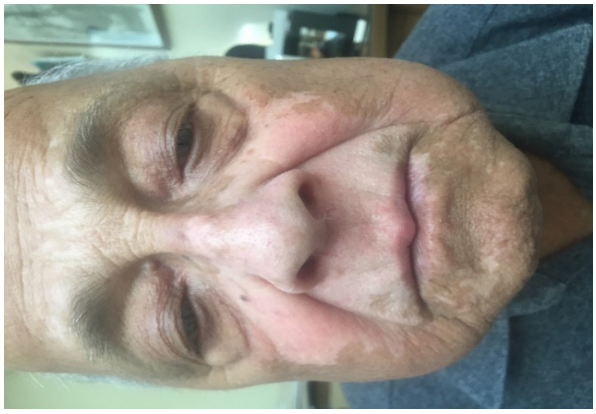
Source: the author.
Figure 1. Patient on the day of admission in August 2016 - Oroscopy - Melanoma in the gingiva and hard palate with invasion of the maxillary sinus before treatment with Nivolumab and radiotherapy



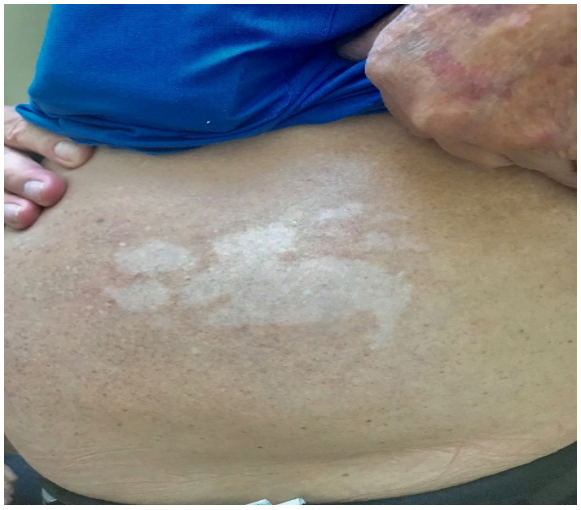
Source: The author
Figure 2. Patient in December 2016 with complete response after starting treatment with Nivolumab and radiotherapy



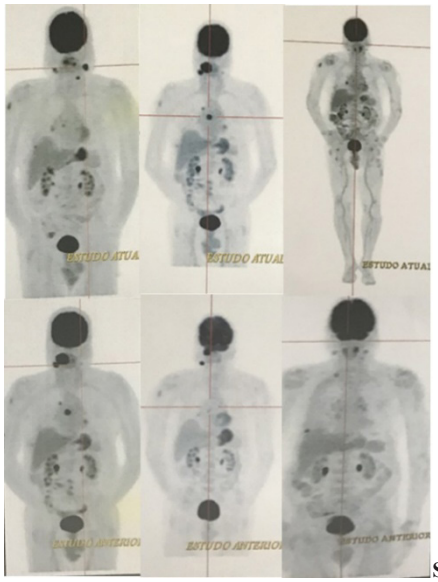
Source: The author
Figure 3. Patient in August 2019 - Full response maintained



Source: The author
Figure 4. Patient in April 2017 - Vitiligo in the face.



Source: The author
Figure 5. Patient in March 2018 - Onset of vitiligo in the flank



Source: The author
Figure 6. PET-CT exams on the admission date in 2016, two years after starting treatment with Nivolumab and radiotherapy (2018), and in August 2019, with response to treatment, from left to right, respectively

DISCUSSION

Primary oral mucosal melanomas (POMM) are neoplasms that originate from mutations of melanocytes, which are the cells responsible for the production of melanin. They were first described by Weber in 1859 and account for 0.2% to 8% of all melanomas and about 0.5% of all malignant neoplasms of the oral cavity[6,9]. They have a higher incidence in China and usually affect individuals in their 5th to 7th decades of life[6,7]. The literature indicates a higher incidence among males, as shown in the case reported here and in a study by Sortino-Rachou et al.[11], which found a prevalence of 54.54% of males in a sample containing 319 individuals. It is believed that the higher incidence among men is due to smoking habits and alcohol consumption[9]. However, some studies indicate a higher incidence among females, as the study by Umeda et al.[12], which found a prevalence of 66.66% of females. In general, its etiology is not specific, and it is currently believed that POMM is associated with intracellular and genetic factors.

The most affected sites are the palate and the gingiva[9]. According to Singh et al.[13], in a total of 1277 patients evaluated in 16 articles included in the meta-analysis, 34.29% had a tumor on the palate, while 8.88% had a neoplasm on the gingiva. Other sites where these lesions can appear include the oral mucosa, tongue, mandible, lips, pharynx and larynx, which are rarer presentations of oral melanoma[6,9]. In this case report, the patient had a tumor in the gingiva and hard palate with invasion of the right maxillary sinus, corroborating the epidemiology reported in the literature.

Melanoma has an asymptomatic onset, difficult visualization, and few clinical signs[1,9,14]. The initial symptom of melanoma is usually a dark macule and edema that progresses to an ulcer on the hard palate[7,15]. The literature suggests that lesions are usually brownish or black macules, with asymmetric and irregular borders [6] [9]. As the disease progresses, symptoms may include pain, tumor, ulcers and bleeding. Metastasis is also common, which partially explains the high mortality rates and the frequent late diagnosis[6,7,14,16].

In this report, the presentation was the most common in the literature: a black and ulcerated tumor, bilateral cervical metastatic lymphadenopathy, and metastasis in the mediastinal lymph nodes and lungs. López et al.[17] found that 25% of the patients with oral cavity melanomas present with lymph node metastases, while Umeda et al.[18] reported that distant metastasis is also common. In an analysis of 35 patients conducted by Tanaka et al.[19], regional and distant metastases occurred in 18 and 23 cases, respectively, and the most distant metastases involved the lungs, which is in agreement with the data found in this report. The results of this study also reinforce the high mortality rates due to late diagnosis, as metastatic disease was already present at the time of the diagnosis of melanoma.

Histologically, the tumor has a wide variety of elements (probably because the disease is usually diagnosed late). An analysis of 32 cases of primary oral melanoma by Smith et al.[1] showed that cell types differ significantly among patients and that most cases displayed a polymorphic cell population, with a greater predominance of epithelioid cells and "spindle cells" (both present in 50% of cases).

The pathogenesis of oral melanoma is complex and involves the interaction between several cytogenetic factors, including the cell cycle, dysregulation of c-KIT signaling, apoptosis, and cell-cell interaction[6,7,9,20]. There is substantial evidence that hyperactive receptor tyrosine kinase (RTK) signaling mediates the development and progression of melanoma. In addition, the c-KIT gene regulates the activity of the microphthalmia-associated transcription factor, which is a leucine transcription factor that is essential for melanogenesis and melanocyte function[6]. Therefore, it is believed that c-KIT alterations produce oncogenic factors that lead to the development of oral melanoma. Mutations in the NRAS or BRAF genes can be found less frequently in these melanomas, as they are more common in cutaneous melanomas[7]. In the case presented, the patient presented with only a c-KIT mutation.

In general, the disease prognosis is poor, worse than skin lesions. The size of the tumor and the presence of metastasis are the main factors that determine the prognosis[6,7,21]. A study conducted by Lopez-Graniel et al.[22] evaluated 15 patients diagnosed with primary melanoma of the oral cavity during a 15-year period and found that the 5-year survival rate was 6.6%, and the only patients who survived free of disease for more than 5 years were those who had a small tumor and no evidence of lymph node metastasis.

The treatment of local oral mucosal melanoma is surgical resection when possible and eventual reconstruction using local flaps. Metastatic lymph nodes in the neck are treated with radical or selective cervical lymphadenectomy[12]. After surgical resection, the use of adjuvant chemotherapy with cisplatin and temozolomide for 6 cycles should be considered.

Radiotherapy after surgery improves local control, but there is no evidence it improves overall survival[23]. In a retrospective study with 160 patients with nonmetastatic head and neck mucosal melanoma treated from 1980 through 2007, Benlyazid et al.[24] evaluated the pattern of recurrence among individuals treated only with surgery and individuals who received radiotherapy after surgery. It was found that the survival rate was the same in both groups, but the local recurrence rate was lower in those who received radiotherapy. In addition, treatment with radiotherapy in the primary lesion of the oral mucosa and other sites can lead to an abscopal effect. This effect is not very common in the clinical area, but it can present itself subtly in radiotherapy treatments and induce distant immune response[25].

Systemic treatment with monoclonal anti-

PD-1 antibodies, immune checkpoint inhibitors and anti-programmed death antibodies (nivolumab and pembrolizumab) is indicated as adjuvant treatment in patients with metastatic lymph nodes and distant metastasis[6,15,20], which justifies the treatment with immunotherapy in this case report. Currently, the literature suggests the associated use of monoclonal antibodies such as anti-PD-1 and anti-CTLA-4 (ipilimumab) as an alternative treatment for advanced cases[20]. Monoclonal antibodies block inhibitory T-cells (CTLA-4) and programmed death 1 (PD-1). PD-1 is part of the CD28 family, and the interaction with its two ligands (PD-L1 and PD-L2) occurs mainly in peripheral tissues, including the tumor environment, leading to apoptosis and downregulation of the effector function of T cells[26]. CTLA-4, on the other hand, is a receptor expressed in T cells that, when interacting with its ligands, inhibits the activity of these cells[27].

These treatments, however, can have immune-related complications such as adrenal insufficiency, hypothyroidism, hepatotoxicity, vitiligo, diabetes, dermatitis, pneumonitis, pituitary metastasis, among others. Among these effects, the patient in this report had adrenal insufficiency, hypothyroidism, vitiligo and diabetes. Adrenal insufficiency occurred in the reports by Sakagushi et al.[20] and Kokkali et al.[28], in which hydrocorticoids were used as treatment. There was also hypothyroidism in the case reported by Kokkali et al., in which hormone replacement therapy was used. The reports by Liu et al.[29], Fukuchi et al.[30], Alzenald et al.[31] and Maekawa, et al.[32] identified vitiligo and diabetes.

Due to its low incidence, results of studies related to the immune treatment of mucosal melanomas are scarce. However, it is currently known that the response to immunotherapy in mucosal melanomas is lower than in skin melanomas[23]. A systematic analysis by D'Angelo et al.[33] evaluated 86 patients with metastatic mucosal melanoma treated only with nivolumab and another 35 patients treated with nivolumab and ipilimumab. The study confirmed that immunotherapy benefits patients in the treatment of the disease, but the objective response rate was relatively low (and lower than the rates obtained in studies involving cutaneous melanoma in general): in monotherapy with nivolumab the response rate was 23.3% and in combination therapy, 37.1%. A study by Shoushtari et al.[34] analyzed 35 patients with mucosal melanoma treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) and found that only 23% of the patients had an objective response. These results not only demonstrate that the immunotherapy response in mucosal melanoma is relatively low, but also indicate greater effectiveness of combined immunotherapy, especially the association between nivolumab and ipilimumab, which has a higher response rate than mono-immunotherapy[23].

According to Tumeh et al.[35], the presence of tumor-infiltrating lymphocytes (TILs) can be an important predictor of the response to anti-PD-1 agents. However, there are few studies that address the prevalence of these lymphocytes in melanomas. Still, according to Song et al.[36], the presence of tumor-infiltrating lymphocytes is apparently associated with a lower risk of metastasis in mucosal melanomas of the oral cavity.

The real reason why the response is lower in mucosal melanomas is not yet known, but it has been hypothesized that response to immunotherapy correlates with the number of mutations in a tumor and its antigen load. As mucosal melanoma is not induced by sun damage, as is the case of cutaneous melanoma, the first is associated with a lower mutational burden and, therefore, poorer response to immunotherapy[23].

The literature suggests that the treatment of advanced melanoma with Nivolumab may bring certain benefits, such as an increased survival rate[37], but highlights its side effects and the need to intervene with corticosteroids to reduce immune-mediated damage[20]. As demonstrated in this report, treatment with Nivolumab induced a significant response to metastatic disease in the patient and had a significant role in the treatment of melanoma, but the onset of side effects in the patient led to the use of corticosteroids (oral prednisone) to treat adrenal insufficiency, levothyroxine to treat hypothyroidism and insulin to treat diabetes (in addition to the presence of vitiligo in the face and left flank).

CONCLUSION

Oral melanoma of the head and neck is a rare tumor, with late diagnosis, more aggressive than cutaneous melanoma, and with a worse prognosis. Current treatment with immunotherapy has shown good results and increased survival even in patients with metastatic disease. In the case presented, the patient had complete locoregional response in the mouth, maxillary sinus, and lymph nodes for more than 3 years, with no evidence of disease progression in the lungs and mediastinal lymph nodes (confirmed by PET-CT). However, there were some immune-mediated complications, which were treated appropriately.

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