J. Oral Diag. 2020; 05:e20200011.

CASE REPORT

Mucosal melanoma: report of case involving the oral cavity

Carla Isabelly Rodrigues-Fernandes [1]*
Amanda Almeida Leite [1]
Ricardo Salgado de Souza [2]
Pablo Agustin Vargas [1]
Halbert Villalba [2]

Abstract:

Primary oral mucosal melanoma (POMM) is a rare neoplasm derived from melanocytes, with unknown aetiology, and different presentation than cutaneous melanoma. It mostly affects the palate and maxillary alveolar ridge, with aspects that may mimic different lesions. Microscopically, POMM is characterized by the presence of medium to large atypical melanocytes with diverse morphologies. This neoplasm still presents challenges with regards to an appropriate treatment, and the overall prognosis is dismal. The aim of this report is to show a case of POMM in a 68-year-old female patient, who was diagnosed due to an extensive and painful oral mass. Although the microscopic diagnosis can be straight-forward for some tumours, most data regarding the biological behaviour of POMM remains uncertain. Detailed microscopic immunohistochemical assessment are essential to elucidate the diagnosis of POMM.

Keywords: Melanoma; Mouth mucosa; Mouth

[1]University of Campinas, Piracicaba Dental School, Department of Oral Diagnosis, Semiology and Pathology Areas, Piracicaba, São Paulo, Brazil.
[2]Paulista University, Department of Dentistry, Sorocaba, São Paulo, Brazil.

Correspondence to:
Halbert Villalba.
E-mail: halbertgv@gmail.com

Article received on May 14, 2020.
Article accepted on July 24, 2020.

DOI: 10.5935/2525-5711.20200011

INTRODUCTION

Mucosal melanomas (MM) comprise a group of rare tumours which originate from melanocytes. Etiological factors of these tumours remains speculative, and they present distinct pathobiology and clinical course in comparison with cutaneous melanomas (Williams; Speight, Wenig, 2017).

Involvement of head and neck accounts for approximately 50% of all cases of MM, where the nasal cavity, paranasal sinuses, and oral cavity are the most affected sites, followed by pharynx and larynx (Lourenço et al, 2014; Green et al, 2017). The tumours present an aggressive clinical behaviour and poor prognosis (López et al, 2016).

Primary oral mucosal melanoma (POMM) accounts for about 0.2-2% of all melanomas, and 0.5% of all malignant neoplasms in the oral cavity (Femiano et al, 2008; Smith et al, 2016; Williams; Speight, Wenig, 2017). This type of melanoma is usually asymptomatic in early stages, and its tumours may mimic different lesions. Thus, prompt recognition and definitive diagnosis is of utmost importance for both clinicians and pathologists (Smith et al, 2016; Green et al, 2017). Considering this scenario, we described a case of POMM and reviewed the literature on this entity.

CASE REPORT

A 68-year-old female patient presented to the oral diagnosis department for evaluation of a painful swelling in the oral cavity, with unknown time of evolution. The patient reported a history of hypertension, which has been treated with an angiotensin-converting enzyme drug. There was no other significant past medical and family history, and the patient denied the use of alcohol and tobacco.

Extraoral examination detected an elevation of the superior lip, and impaired occlusion of the patient. Intraoral examination revealed an extensive, ill-defined, broad-based, reddish-purple soft tissue mass, containing focal areas of ulceration and black-purple colour, presenting irregular surface, and fixation to the underlying tissue. The lesion caused complete effacement of the anterior vestibule, and extended to the palate and superior alveolar ridge (Figure 1). Palpation of the mass did not show any bleaching.

An incisional biopsy of the lesion was performed under local anaesthesia, and microscopic examination demonstrated a stratified squamous parakeratinized epithelium in the surface, with areas of ulceration. The subjacent connective tissue exhibited several invasive nests and small sheets of pleomorphic cells, with plasmacytoid, rhabdoid, ovoid, and epithelioid morphology. (Figures 2A-C). The nucleous:cytoplasm ratio was variable among the neoplastic cells, which mostly presented vesicular nuclei and prominent nucleoli. (Figure 2D). A chronic inflammatory infiltrate was also observed, mainly composed of lymphocytes (Figure 2E). Atypical mitotic figures were evident, while melanin was minimally identified at high-power view (Figure 2F).

Immunohistochemical reactions confirmed the melanocytic tumour origin with a diffuse and strong positivity for HMB45 (clone HMB-45; dilution 1:200; Dako, Carpinteria, CA, USA) [Figure 3A], and Melan-A (clone A103; dilution 1:800; Dako, Carpinteria, CA, USA) [Figure 3B]. Proliferative index demonstrated by Ki67 staining was high (clone MIB-1; dilution 1:100; Dako, Carpinteria, CA, USA) [Figure 3C]. These histological sections were exposed to high-sensitive horseradish peroxidase reagents (ADVANCE, Dako, Capinteria, CA, USA) and diaminobenzidine tetrahydrochloride (DAB, Sigma-Aldrich, St Louis, MO, USA). The slides were counterstained with Carazzi hematoxylin. Considering

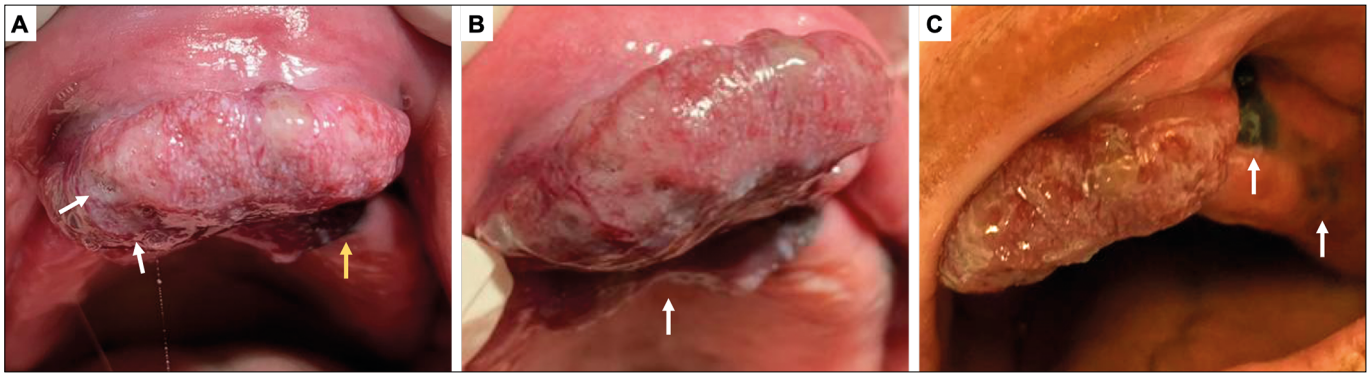

Figure 1. Clinical presentation of the case. A: A diffuse swelling involving the anterior vestibule and superior alveolar ridge. Small areas of ulceration are observed (white arrows). Posteriorly, a dark-colour surface is also noted (yellow arrow). B: Extension of the tumour to the hard palate, affecting both right and left sides (white arrow). C: Left gingival surface demonstrating other stained areas (white arrows).

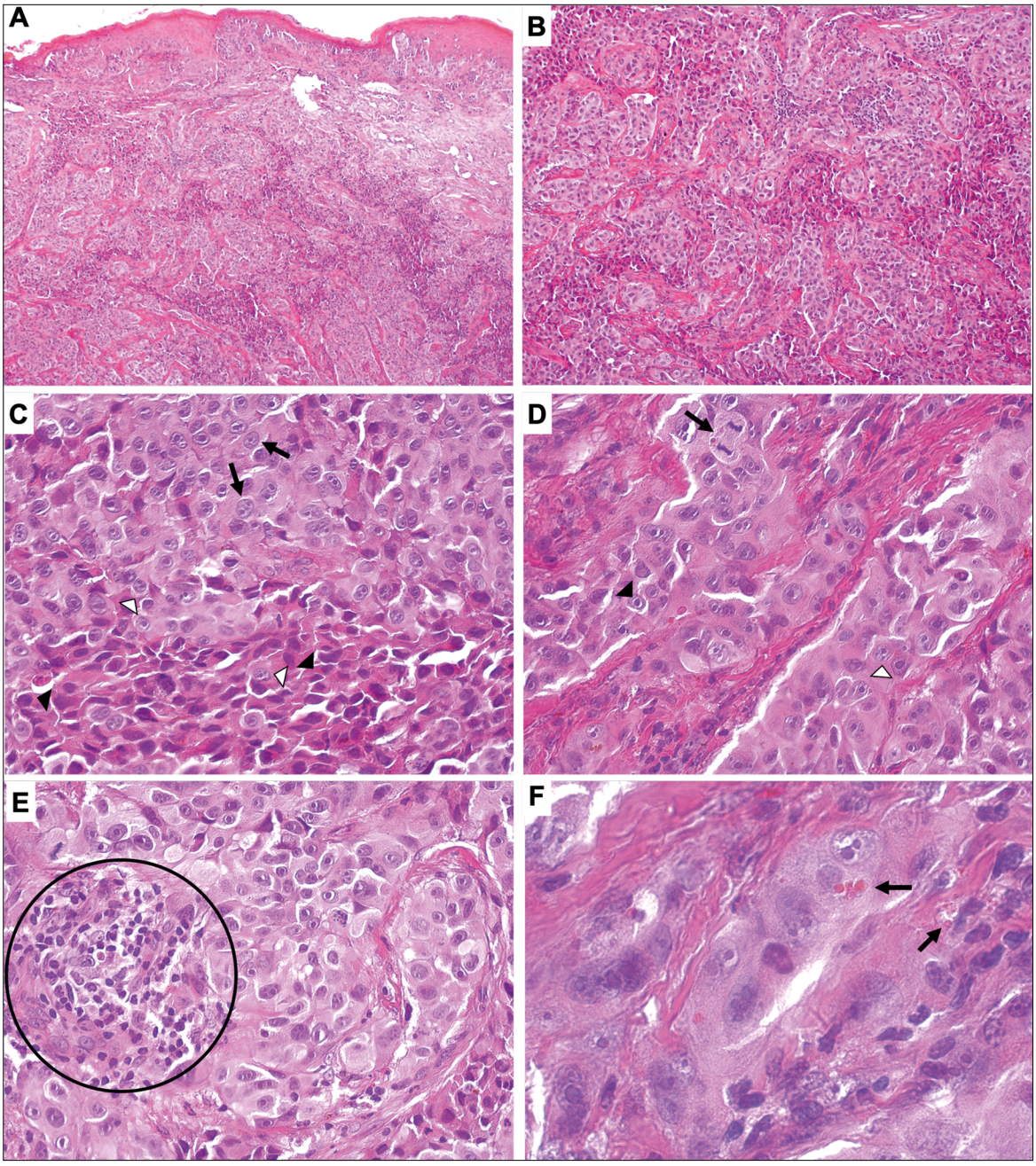

Figure 2. Microscopic features of the tumour. A: Invasion and enfacement of the connective tissue with sheets and nests of neoplastic cells (H&E, 100x). B: High-power view of fibrous septa separating nests of atypical melanocytes (H&E, 200x). C: Variable phenotype of neoplastic cells, which exhibited epithelioid (black arrow), plasmacytoid (white triangle), and rhabdoid morphology (black triangle) [H&E, 400x]. D: Most cells presented vesicular nuclei, with prominent nucleoli (black triangle) and dispersed chromatin (white triangle). An atypical mitotic figure was also observed (black arrow) [H&E, 400x). E: Focal area of chronic inflammatory infiltrate, mostly composed by lymphocytes (H&E, 400x). F: High-power view showing melanin (black arrows) [H&E, 1000x].

all findings, a diagnosis of malignant POMM was established, and the patient was referred for immediate oncologic treatment.

DISCUSSION

The presence of melanocytes within the oral mucosa is observed from 20 weeks in utero, and their role

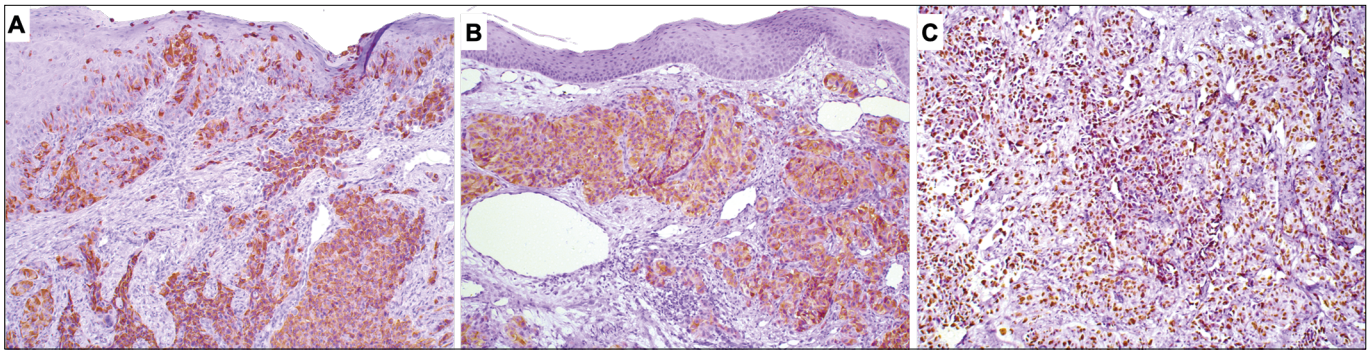

Figure 3. Immunohistochemical findings of the tumour. A-B: Strong cytoplasmatic positivity of HMB45 (A) and Melan-A (B) markers, highlighting the melanocytic origin of neoplastic cells (DAB, 100x). C: High proliferative index demonstrated by nuclear Ki67 staining (DAB, 100x).

is likely to be related to immunologic processes (López et al, 2016). It is likely that the malignant transformation of melanocytes in primary MM results from sequential accumulation of genetic and molecular modifications, which alter intracellular signalling cascades (Kaufman et al, 2013; Green et al, 2017). Associated mutations include cKIT, NRAS, GNAQ, MYC, Cyclin D1, and BRAF genes (Rivera et al, 2008; Carvajal et al, 2011; Ascierto et al, 2017). Smoking and drinking habits, as well as local tissue irritation have been postulated as risk factors for MM, however these correlations have not been elucidated (Femiano et al, 2008; Ascierto et al, 2017). Moreover, it has been suggested that POMM arises from pigmented nevi, pre-existing pigmented areas, or racial pigmentation, although most cases arise de novo, which seems to be related to our case (López et al, 2016; Mikkelsen et al, 2016).

Melanoma of the oral cavity presents a broad age range (9-91 years), with a peak incidence in the sixth decade of life, and a rare occurrence in individuals younger than 30 years (Lourenço et al, 2014; López et al, 2016; Williams; Speight, Wenig, 2017). There seems to be no consensus regarding sex prevalence, since some studies reported a female predominance (Guevara-Canales et al, 2012; Smith et al, 2016), while others described more cases in males (McLean et al, 2008; Wang et al, 2012). Still, a series of 35 cases of POMM found an equal distribution between males and females (Lourenço et al, 2009). In accordance with the present case, most oral melanomas affect the maxillary alveolar ridge and/or the hard palate (Green et al, 2017), even though some authors reported involvement of the buccal mucosa (Breik et al, 2016; Chatzistefanou et al, 2016), tongue (Guevara-Canales et al, 2012; Smith et al, 2016); floor of the mouth (Lourenço et al, 2009), and lips (Lamichhane et al, 2015).

The tumours frequently manifest as a macular or nodular pigmented lesion, which can be uniformly brown or black, or exhibit variable pigmentation ranges of black, brown, purple, and grey colours. Amelanotic melanomas usually exhibit red or pink appearance (Mohan et al, 2013; Rawal et al, 2017). Pigmented small lesions can be initially interpreted as racial pigmentation, melanotic macule, amalgam tattoos, smoker's melanosis, oral melanoacanthoma, and nevi (Femiano et al, 2008; Topić et al, 2017). Other benign and malignant lesions have also been considered, such as fibrous hyperplasia, pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, and Kaposi's sarcoma (Chatzistefanou et al, 2016). Considering that POMM is initially asymptomatic and generally unnoticed by patients, diagnosis in advanced stages is frequent, with an average of 5.6 months between the appearance of the first symptoms and time of diagnosis (Femiano et al, 2008; McLean et al, 2008). Advanced tumours can present exophytic, asymmetric, and irregular growths with spontaneous bleeding, pain, ulceration, and tooth mobility, and may have satellite adjacent lesions (Breik et al, 2016; López et al, 2016). To rule out these differential diagnoses, the ABCDE checklist (A – asymmetry; B – border irregularities; C – colour variegation; D – diameter > 6 mm; E – elevation) can be helpful, despite its widely use for cutaneous melanoma (Mohan et al; 2013).

Microscopic characteristics of POMM comprise a proliferation of medium to large neoplastic melanocytes with diverse phenotypes, including epithelioid, spindle, clear, and plasmacytoid cells, which can be arranged in sheets, organoid, alveolar, solid or desmoplastic architecture (Chatzistefanou et al 2016; Ascierto et al, 2017). Mitotic activity is variable, as well as the presence of melanin on haematoxylin and eosin staining (Green et al, 2017). Considering this polymorphism of non-epithelial

cell population, cases which exhibit a malignant proliferation with more than one cell type should include melanoma as a the main diagnostic hypothesis (Smith et al, 2016). However, several different diagnoses should be addressed in cases of amelanotic lesions, including undifferentiated squamous cell carcinoma, non-Hodgkin lymphoma, rhabdomyosarcoma, plasmacytoma/multiple myeloma, metastatic renal cell carcinoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma (López et al, 2016; Green et al, 2016). Thus, immunohistochemistry is essential; POMMs are typically positive for S-100 protein, vimentin, and the melanocytic markers HMB-45 and Melan-A, and negative for cytokeratin and epithelial membrane antigen (Lourenço et al, 2014). The combination of Ki67 and HMB-45 is helpful to distinguish the malignant nature of the tumour, and to evaluate its growth pattern (Mikkelsen et al, 2016).

Staging and classification for MMs remains without consensus, since the proposed systems are still limited to either clinical or microscopic patterns, and there is no general standardization. The 8th edition of the American Joint Committee on Cancer Staging Manual (2017) has proposed a specific version of the Tumour-Node-Metastasis (TNM) classification for head and neck MM. However, there is lack of prognostic stage grouping, and there is no recommended histologic grading system, as well as prognosis distiguishing according to microscopic differences (Lydiatt et al, 2017). An earlier, more simple system categorized the tumours in 3 microscopic stages, comprising localised lesions, cervical lymph node metastasis and distant metastasis, without considering the depth of invasion or local tumour extension (Ballantyne, 1970). Furthermore, a 3-level micro-staging system classified MMs as in situ, superficially, and deeply invasive within the mucosa, although this method only relies on specimens obtained after surgical excision (Prasad et al, 2004).

Treatment of POMM is mainly surgical, which encompasses different types of maxillectomy, mandibulotomy, and mandibulectomy, according to the tumour's site and extension, with disease-free tissue margins (Green et al, 2017). Conversely, the proximity of vital structures, such as venous plexus, great vessels, and cranial nerves often precludes an accurate local control (Mohan et al, 2013; Chatzistefanou et al 2016). Additionally, local, regional or distant recurrence of head and neck MM remains a common event, regardless of surgical resection (Ascierto et al, 2017). The use of radiotherapy has been indicated in cases with positive surgical margins, multiple nodal involvement, advanced and unresectable tumours, and those which requires palliative treatment, as well as chemotherapy (Breik et al, 2016; López et al, 2016; Rawal et al, 2017). The prognosis of POMM is extremely poor, with lower survival rates in comparison with other melanomas; the median overall survival is no longer than 2 years, and mean rate after 5 years is less than 30% (Chatzistefanou et al 2016; Williams; Speight, Wenig, 2017). Amelanotic tumours tend to present a worse prognosis, as they are usually diagnosed at advanced stage (Breik et al, 2016; Green et al, 2017).

In summary, POMM is uncommon, with different clinical presentation and course in comparison with other subtypes of melanoma, being usually detected in an advanced stage. Given the scarcity of MMs involving the oral cavity, most available information relies on case reports and case series. Thus, early and careful clinical, microscopic and immunohistochemical evaluation remains crucial.

Acknowledgments

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Williams MO, Speight P, Wenig BM. Oral mucosal melanoma. In: EI-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. WHO classification of Head and Neck Tumours. 4th Edition. Lyon: IARC; 2017. p. 126-7.
2. Lourenço SV, Fernandes JD, Hsieh R, Coutinho-Camillo CM, Bologna S, Sangueza M, et al. Head and neck mucosal melanoma: a review. Am J Dermatopathol. 2014 Jul;36(7):578-87.
3. Green B, Elhamshary A, Gomez R, Rahimi S, Brennan PA. An update on the current management of head and neck mucosal melanoma. J Oral Pathol Med. 2017 Jan;46(7):475-9.
4. López F, Rodrigo JP, Cardesa A, Triantafyllou A, Devaney KO, Mendenhall WM, et al. Update on primary head and neck mucosal melanoma. Head Neck. 2016 Jan;38(1):147-55.
5. 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 Aug;37(7):383-8.
6. Smith MH, Bhattacharyya I, Cohen DM, Islam NM, Fitzpatrick S, 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 Jan;10(3):298-305.
7. Kaufman HL, Kirkwood JM, Hodi FS, Agarwala S, Amatruda T, Bines SD, et al. The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. Nat Rev Clin Oncol. 2013 Oct;10(10):588-98.

8. Rivera RS, Nagatsuka H, Gunduz M, Cengiz B, Gunduz E, Siar CH, et al. C-kit protein expression correlated with activating mutations in KIT gene in oral mucosal melanoma. Virchows Arch. 2008 Jan;452(1):27-32.
9. Meng D, Carvajal RD. KIT as an oncogenic driver in melanoma: an update on clinical development. Am J Clin Dermatol. 2019 Jun;20(3):315-23.
10. Ascierto PA, Accorona R, Botti G, Farina D, Fossati P, Gatta G, et al. Mucosal melanoma of the head and neck. Crit Rev Oncol Hematol. 2017 Apr;112:136-52.
11. Mikkelsen LH, Larsen AC, von Buchwald C, Drzewiecki KT, Prause JU, Heegaard S. Mucosal malignant melanoma – a clinical, oncological, pathological and genetic survey. APMIS. 2016 Jun;124(6):475-86.
12. Guevara-Canales JO, Gutiérrez-Morales MM, Sacsaquispe--Contreras SJ, Sánchez-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 Mar;17(2):e206-11.
13. McLean N, Tighiouart M, Muller S. Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. Oral Oncol. 2008 Apr;44(11):1039-46.
14. Wand X, Wu HM, Ren GX, Tang J, Guo W. Primary oral mucosal melanoma: advocate a wait-and-see policy in the clinically N0 patient. J Oral Maxillofac Surg. 2012 May;70(5):1192-8.
15. Lourenço SV, A MS, Sotto MN, Bologna SB, Giacomo TB, Buim ME, et al. Primary oral mucosal melanoma: a series of 35 new cases from South America. Am J Dermatopathol. 2009 Jun;31(4):323-30.
16. Breik O, Sim F, Wong T, Nastri A, Iseli TA, Wiesenfeld D. Survival outcomes of mucosal melanoma in the head and neck: case series and review of current treatment guidelines. J Oral Maxillofac Surg. 2016 Sep;74(9):1859-71.
17. 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 Jul;122(1):17-27.
18. 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 Sep;8:499.
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 Oct;116(4):e247-54.
20. Rawal YB, Dodson TB, Bal HS. Oral melanoma: relevance to the dental members. J Am Dent Assoc. 2017 Feb;148(2):113-9.
21. Topić B, Mašić T, Radović S, Lincender I, Muhić E. Primary oral mucosal melanomas – two case reports and comprehensive literature review. Acta Clin Croat. 2017 Jun;56(2):323-30.
22. Lydiatt WM, Brandwein-Gensler M, Kraus DH, Mukherji SK, Ridge JA, Shah JP. Mucosal melanoma of the head and neck. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., eds. AJCC - Cancer staging manual. 8th ed. New York: American Joint Committee on Cancer (AJCC)/ Springer International Publishing; 2017. p. 163-9.
23. Ballantyne AJ. Malignant melanoma of the skin of the head and neck. An analysis of 405 cases. Am J Surg. 1970 Oct;120(4):425-31.
24. Prasad ML, Patel SG, Huvos AG, Shah JP, Busam KJ. Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, stage I (lymph node-negative) tumors. Cancer. 2004 Apr;100(8):1657-64.