# PRIMARY ORAL MALIGNANT MELANOMA: CASE REPORT

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SUMMARY – Primary oral malignant melanoma usually presents as a dark brown or black lesion. It is a rare malignancy, accounting for less than 1% of all melanomas and 1.6% of all head and neck malignancies, thus forming up to 0.5% of all oral malignancies in the world literature. In general, the prognosis of oral melanoma is poor and worse than that of cutaneous melanoma. The preferred treatment is radical surgery alone or in combination with radiotherapy, chemotherapy, immunotherapy and immunomodulatory agents. A case is presented of a large malignant melanoma of oral cavity, noticed six months before initial biopsy and by history described as a rapidly growing mass.

Key words: *Mouth neoplasms – diagnosis; Mouth neoplasms – pathology; Mouth neoplasma – surgery; Melanoma – diagnosis; Melanoma – pathology; Melanoma – surgery*

## Introduction

Melanomas of oral mucosa are fortunately rare. Primary oral malignant melanoma (POM) usually presents as a dark brown or black lesion, however, 15% of POMs are non-pigmented and typically red lesions, thus presenting as amelanotic melanomas that mimic some other oral mucosa red lesions[1-5]. Because of their rare occurrence, malignancies of this type are poorly documented in the literature. Most information on its clinical, epidemiologic and histopathologic features comes from small series of cases describing deep extension with or without bone invasion. Although there is no racial predilection, Afro-Americans and Asians appear to be proportionately more commonly affected than Caucasians[4,6]. The development of POM in relatively obscure areas of the oral cavity is the reason why it is diagnosed in a late stage at this location. The majority of POM cases develop on the head and neck mucosal surfaces (55%). It is a rare malignancy, accounting for less than 1% of all melanomas and 1.6% of all head and neck malignances, thus forming up to 0.5% of all oral malignancies in the world literature[1-4]. Approximately half of them are located in the oral cavity, placed on the palate and maxillary gingiva as the most frequently affected sites, with maxillary arch being affected in 80% of cases[2,4,6]. Dental clinicians play a major role in the identification of pigmented lesions of oral cavity[4]. Therefore, any pigmented lesion detected in the oral cavity that may exhibit potential growth should be submitted to biopsy to exclude malignancy[1,4]. In 2005, the incidence of gingival, soft palate and oropharyngeal POM in the Croatian population was 0.5, 0.3 and 1.1 *per* 100 000, respectively[5]. This malignancy is a lesion of adulthood, rarely occurring under the age of 20 years, with the peak incidence between 40 and 60 years of age[2,4,7-9]. POMs more commonly affect male patients, with a male to

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female ratio ranging between 1:1 and 3:1 in different studies[2,4,7-10].

## Case Report

A 51-year-old male Caucasian was admitted to the hospital because of a painful mass on the left side of oral cavity. The patient noticed the growing mass some six months before presentation. Intraoral physical examination revealed an elevated, nodular, grey and slightly dark pigmented, erosive lesion of irregular borders, measuring up to 10 cm in diameter. The tumor was located on the left side of the tongue infiltrating the left tonsil, hard and soft palate and left maxillary canine region, extending through oral cavity to its right side and to the oropharynx (Fig. 1). Incisional biopsy was performed. Histopathologic hematoxylin-eosin stained biopsy sections showed oral stratified squamous epithelium with a malignant neoplasm. It comprised of sheets and fascicles of atypical, heavily pigmented melanocytes spindle or ovoid in shape. The malignant melanocytes had hyperchromatic polymorphic nuclei and high nucleocytoplasmic ratio exhibiting numerous mitoses (Fig. 2). We used antibodies for routine diagnosis of melanoma (HMB-45), which produced intensive staining of tumor cells (Fig. 3), and in addition Melan-A, vimentin and Ki-67 (photograph is not available due to the very small size of the specimen and thus poor reaction). On differential diagnosis, we used keratin and epithelial membrane antigen (EMA), which showed no expression on tumor cells, thus confirming the melanocytic nature of the lesion. The lesion was diagnosed pathologically as oral melanoma. The tumor extended deep into the connective tissue but not in the underlying bone. Surgical treatment was not possible because of the large size of the tumor. Radiotherapy by Mavathron for three weeks on two reverse fields with 6 mega electron volts was initiated two months of the initial biopsy. Nuclear magnetic resonance (NMR) performed one

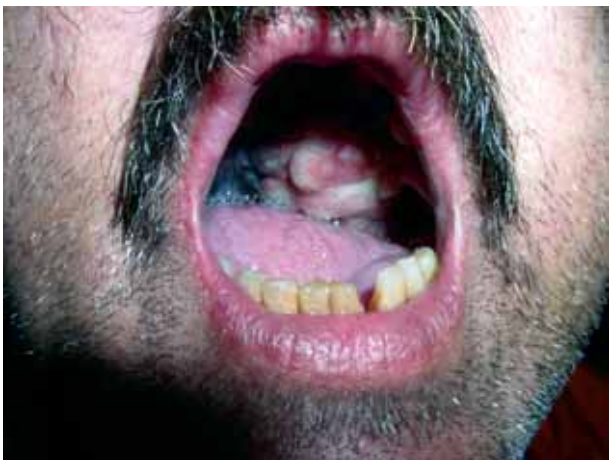

*Fig. 1. Physical examination revealed a large, dark, nodular, proliferative tumor growth on the left side of the tongue, infiltrating the left tonsil, hard and soft palate, and maxillary canine region.*

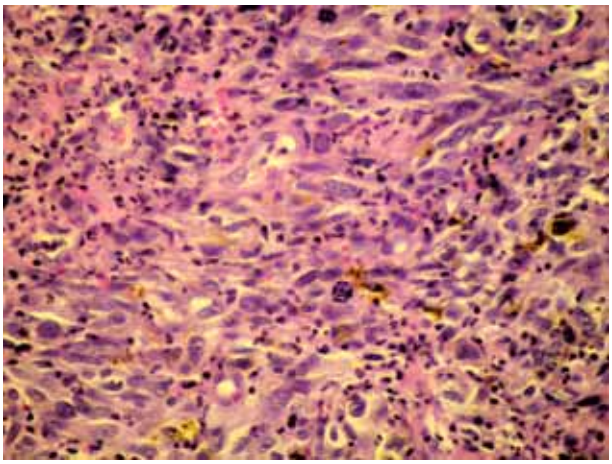

*Fig. 2. Photomicrograph showing infiltration with numerous atypical pleomorphic melanocytes containing brownish-black granular pigment in the cytoplasm (H&E, X400);*

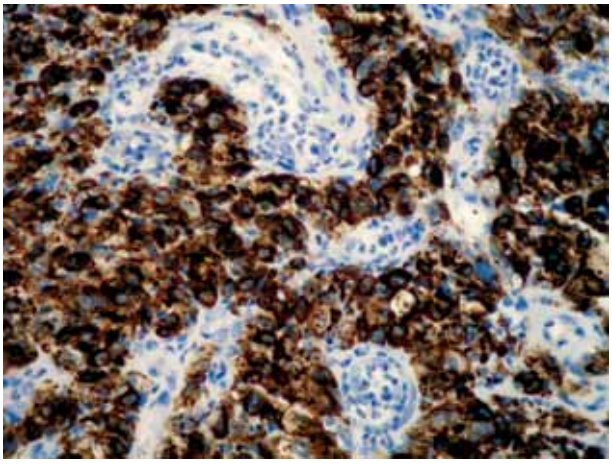

*Fig. 3. Tumor showing intense HMB-45 positive reaction in malignant melanocytes (X400).*

month after radiotherapy showed that there was no invasion of thoracic and abdominal lymph nodes and organs. Follow up examination at six months revealed partial regression of the tumor on the hard palate and left buccal mucosa. Isthmus faucium was completely obstructed by the round tumor mass measuring up to 6 cm in diameter. The submandibular area revealed conglomerates of lymph nodes measuring up to 7x4 cm bilaterally. Subjectively, the patient denied pain in the oral cavity. Eight months later, the patient was still on therapy. Ten months after the first diagnosis, he was hospitalized, accepting only pain killers and refused the immunotherapy proposed. Ten months later, the patient died. The exact cause of death was not established because autopsy was not performed.

## Discussion

Oral cavity is a common site of various brown or black pigmented lesions, e.g., amalgam tattoo, pigmented nevi, Addison's disease, Peutz-Jeghers syndrome, racial pigmentation melanotic macules associated with HIV infection, smoker melanosis, drug-induced pigmentation and melanoma[1,4]. Most pigmented lesion are benign, but despite the rarity of the disease, POM is the most important pigmented lesion in the oral cavity because of its deadly nature and must be diagnosed in time. Most if not all oral biopsies of pigmented lesions are aimed at excluding malignant melanoma[1,4,11]. If diagnosed early, when the malignant cells are limited to the epidermis or the invasion is minimal, cutaneous melanoma is either 100% curable by excision or is associated with a 5-year survival rate of 95% *versus* 45% for a similar melanoma thicker than 4 mm[1,12-16]. The prognosis of POM is much worse, with 5-year survival rates generally ranging from 10% to 25%, or according to some authors 15%-38%, partly because of difficulties to detect pigmented lesion and poor resectability due to the anatomy of the region, major extension in depth *versus* cutaneous melanoma, and early metastasis[1,8]. The median survival for all POMs is slightly over 2 years (18-46 months) from the time of diagnosis, depending on lymph node involvement, increased tumor thickness, and level and vertical growth phase of the tumor at the diagnosis[8,16-21]. POM is an uncommon malignant tumor that originates from melanocyte proliferation. During embryologic development, melanocytes migrate from neural crest into the epithelial lining of the skin. As the oral cavity develops from an ectodermal depression or invagination, the epithelial lining of oral mucosa, similar to the skin, contains melanocytes in its basal layer[1,2,4]. Some authors suggest that there are more than one biologic type of oral melanoma, i.e. invasive (without significant lateral spread) and *in situ* subtype undergoing a junctional growth phase that may last for months to years before entering the vertical growth phase[4]. A third term, atypical melanocytic proliferation, has been used in relation to difficult macroscopic detection of oral pigmentation when the presence of unusual numbers of melanocytes with abnormal morphology at the epithelium-connective tissue interface is detected[4,20,21]. POM is usually asymptomatic in the early stages, presenting as a pigmented patch or rarely as a mass with a rapid grow rate. We report a case where the patient's underestimation of his symptoms, probably due to its painless character, was the main reason for not seeking medical care in time. He presented in an advanced stage of the disease. Generally, the lesion can be flat (macula) or elevated (nodule or exophytic), with or without ulceration or erythematous border[1-4]. In the advanced stage, it can show ulceration, swelling, bleeding, rapid enlargement and tooth loosening[1,2,11]. Clinically, tumors are classified in five types: 1) pigmented nodular; 2) non-pigmented nodular; 3) pigmented macular; 4) pigmented mixed; and 5) non-pigmented mixed type[1,2]. Approximately half of POMs in the oral cavity are located on the palate and maxillary gingiva as the most frequently affected sites[2,4,16,17]. In contrast to the well established etiologic factors for skin melanoma, the causative factors of POM such as family history, syndromes, and cytogenetic defects have not been studied extensively[2,10]. The International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) and World Health Organization (WHO) have not yet proposed clinical TNM classification for malignant melanomas and guidelines for POM staging either[16,18,21-24]. The Clark grading system assessing the depth of invasion and Breslow measuring the thickness of the tumor from the surface of the epidermis to the greatest depth of the tumor have no validation as prognostic factors in POMs due to the rarity of this lesion. In 2004, some

authors proposed a clinical staging system with histopathologic microstaging in three levels for stage I (with no regional lymph node metastases), cited in several review articles[10,12,21,22,25]. The common sites of metastases are lymph nodes, liver and lungs, with wide dissemination in the advanced disease[12,14,26,27]. Surgery is the mainstay of treatment, but it is often difficult to perform because of the anatomic region features. Although melanoma is classically not very radiosensitive, patients have occasionally had good response to radiotherapy, especially in melanoma *in situ* and in cases with very poor prognosis when surgery is rejected. Adjuvant radiotherapy to the primary location, immunotherapy (interferon alpha-2b) and chemotherapy (dacarbazine-DTIC), along with immunomodulatory agents such as bacilli Calmette-Guérin (BCG) and recombinant interleukin-2 (rIL-2), may be combined with surgery[3,13-18,20]. The prognosis of melanoma is poor, with a mean 5-year survival after resection of 5% to 38%, 26% when the lesion was confined to the primary site, and declining to 0% in the presence of regional lymph node or distant metastases. The importance of this malignancy lies in its high aggressiveness, with a 5-year survival rate ranging from 10% to 25% in the literature[1-4,17-19]. Inadequate resection of the margins and a higher stage at initial diagnosis may contribute to this poor rate of survival[18].

Although the prognosis of oral melanoma is generally poor, the early identification and initial biopsy of pigmented oral lesion should be done to exclude the presence of oral melanoma. Patient's compliance is of utmost importance in detecting oral pigmented lesions, along with appropriate physician's and dentist's diagnostic skills supported by histology confirmation[1,2,10,24,28,29]. Early diagnosis of oral melanoma is more important for successful treatment than at any other primary site and is one of the key factors for better prognosis; unfortunately, it remains unproven because of the small number of cases. In case of high clinician's suspicion, repeat biopsies should be performed irrespective of the possibly benign features shown on initial biopsy. Analysis of published cases and recognition of new ones may be helpful in establishing definite classification and proposing clinical features that would facilitate its early diagnosis as a prerequisite for timely treatment and better prognosis of this rare pathology[30].

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Sažetak

## PRIMARNI ZLOĆUDNI MELANOM SLUZNICE USNE ŠUPLJINE

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Primarni melanom sluznice usne šupljine obično je tamno smeđe ili crno pigmentirana lezija. Vrlo je rijetka zloćudna bolest koja se javlja u manje od 1% svih melanoma i čini 1,6% svih maligniteta glave i vrata tvoreći, kako navodi svjetska literatura, do 0,5% svih maligniteta u usnoj šupljini. Općenito, prognoza je lošija nego kod kožnih melanoma. Kirurška resekcija je jedan od najčešćih oblika liječenja, a pokušava se i radioterapijom, kemoterapijom, imunoterapijom i imunomodulatorima. Opisuje se slučaj velikog melanoma u usnoj šupljini ubrzani rast kojega je primijećen šest mjeseci prije biopsije i potvrđene dijagnoze.

Ključne riječi: *Novotvorine usne šupljine – dijagnostika; Novotvorine usne šupljine – patologija; Novotvorine usne šupljine – kirurgija; Melanom – dijagnostika; Melanom – patologija; Melanom – kirurgija*