PRIMARY ORAL MUCOSAL MELANOMAS – TWO CASE REPORTS AND COMPREHENSIVE LITERATURE REVIEW

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SUMMARY – Oral melanoma (OM) occurs from activated or genetically altered epidermal melanocytes. There is no scientific evidence that OM can be linked to physical, chemical and thermal irritation, or to other risk factors of the oral cavity. According to figures from various countries, OM accounts for 0.2% to 7.5% (Japan) of all cases of melanoma of the skin and mucous membrane. The male to female ratio of OM is 2:1. About 80% of OMs are located in the mucosa of the palate and maxillary gingiva. This paper presents two cases of oral mucosal melanoma of the upper and lower lips in women aged 62 and 59 years. Diagnosis, differential diagnosis and therapy are reported.

Key words: *Melanoma – pathology; Mouth neoplasms – diagnosis; Mouth neoplasms – therapy; Case reports*

Introduction

Melanoma as a malignant lesion can occur from activated or genetically altered epidermal melanocytes. Activation of melanocytes is a result of complex interactions among genetic, constitutional and environmental factors[1]. In contrast to skin melanoma, the etiology of which in most cases is related to ultraviolet light, this risk factor does not exist for oral melanoma (OM). There is no scientific evidence that OM can be linked to physical, chemical and thermal irritation, or to other risk factors in the oral cavity, for example, alcohol, poor oral hygiene, caries and damaged teeth, prosthetics and other irritations to which oral cavity is constantly exposed. Formaldehyde and smoking are listed as risk factors. In workers professionally exposed to formaldehyde fumes, cases of sinonasal melanomas have been reported[2]. Swedish authors mention the more prevalent pigmentation of oral mucosa in smokers, deeming it to be a risk factor for OM[3]. Knowledge of the etiology of OM comes mainly from epidemiological studies, but these risk factors for OM have not been confirmed by scientific evidence. It is thought that after dysplastic nevus, as a precursor, some OMs occur *de novo*[4]. The physiological accumulation of melanin pigmentation in melanocytes is manifested clinically in a variety of efflorescence on the skin, mainly moles and freckles. When melanin is formed and accumulated in melanocytes with malignant characteristics, melanomas occur. Melanomas may develop from preexisting pigmentation of the skin and mucosa, but some occur *de novo*.

For melanomas of the head and neck, Virag lists three types and gives their quantification[5]. They are: superficial spreading melanoma (SSM), which occurs in about 70% of patients; nodular malignant melanoma (NM), which occurs in about 15% of patients; and lentigo maligna melanoma (LMM), which occurs in about 15%, in older patients, on the exposed parts of the body on the basis of premalignant melanosis as the result of chronic exposure to sunlight; according to the personal

clinical experience of Professor Virag, acral melanomas do not occur on the skin of the head and neck[5].

Melanomas of the skin are located in the area of the face and the front of the hair, accounting for most melanomas of the face and neck, and are related to lymph nodes in the parotid region[6]. In the superficial lobe of the parotid gland, there are 2 to 10 lymph nodes, but half as many nodes lie medially to the facial nerve. Surgery of the parotid gland is complicated by the facial nerve and its branches *(pes anserinus)*. Surgery of the parotid is said to be in fact surgery of the facial nerve[7]. Facial nerve has an important functional, aesthetic, operational, communication and social value.

The microscopic spread of melanoma develops in two directions, i.e. horizontally, radially (mainly related to the epidermis), and vertically, invasively (related to deeper structure of the skin and mucosa, dermis, subcutis, blood and lymph vessels)[8].

The degree of invasiveness of a skin melanoma is determined histopathologically, using the Breslow[9] or Clark[10] criteria.

Breslow proposees direct measurement of tumor thickness using calibrated ocular micrometer. The maximum vertical diameter of the tumor is evaluated, which represents the distance from the tip of the granulated layer of the epidermis and deepest point of tumor cell infiltration, and if the lesion is ulcerated, then from the base of the ulcer to the deepest point of tumor invasion. According to this criterion, there are 4 stages of invasiveness[9]. The Clark criteria have five stages of invasiveness[10].

Characteristics of Oral Melanomas

In contrast to the skin, it is more difficult to differentiate by microscope the papillary layer from the reticular layer in the oral mucosa, which means that the Clark criteria are not applicable for oral mucosa. Routine diagnostics of the depth or thickness of tumors, as defined by Clark and Breslow, has not been accepted in everyday practice for OM, due to these structural differences between the skin and the oral mucosa. For example, five-year survival with gingival melanoma was 18%, and with melanoma of the palatal mucosa 11%[11]. Most melanomas of the mucosa of the head and neck at the time when they are presented, are in stage I. Prasad *et al.*[12] defined this status using a 3-level micro-staging system, which represents differ-

ent micro-anatomic spaces of the separate tissue barriers. These are a significant predictor related to 5-year survival[12,13]. The American Joint Committee on Cancer (AJCC) Melanoma Staging Committee, in its already existing guide to melanoma, updated the criteria in the final version of the Tumor-Node-Metastasis (TNM) classification of melanoma[14]. However, in this updated version of the TNM classification of melanomas, the AJCC did not define criteria for mucosal melanomas because no universal staging system exists for them. Different staging systems are in use for different anatomic locations[15]. In the assessment of oral mucosal melanomas, a simplified system is used including three stages, as follows: stage I, primary localization of disease; stage II, primary disease with metastasis to cervical lymph nodes; and stage III, distant metastasis[8].

As already mentioned, in stage I, a 3-level micro-staging system has been defined, where each level represents a micro-anatomic space, defined by tissue boundary. Destruction of any barrier (boundary) of that space correlates with progressive deterioration of survival rates. Stage I has 3 levels: Level 1, *in situ* mucosal melanoma or microinvasion: Level 2, invasion restricted to the lamina propria; and Level 3, melanoma with deep invasion into the neighboring tissue, such as bone (in the oral mucosa), cartilage (in the larynx), or skeletal muscle[12,13].

The superficial architecture of oral melanomas is seen in macular, ulcerous or nodular forms.

According to the recommendation by the Western Society of Teachers of Oral Pathology (WESTOP) Banff Workshop, oral malignant melanomas should be considered separately from skin melanomas and subclassified according to the histopathologic picture as *in situ* melanomas; invasive melanomas; combined: invasive melanomas with *in situ* components; and atypical melanocyte proliferation, in cases where there is an equivocal histologic diagnosis[16].

Japanese and Mexican authors suggest that OM differs from skin melanoma from the point of view of the clinical picture, etiology and malignancy. They propose 5 types of OM for the clinical picture: pigmented nodular type; non-pigmented nodular type; pigmented macular type; pigmented mixed type; and non-pigmented mixed type[17,18].

Clinical verification of OM meets the ABCDE rules from the Anglo-Saxon and German dermatology literature: A, asymmetry; B, border irregularity; C,

color variation; D, diameter >6 mm; and E, elevation[19-21].

This typical clinical characterization of melanomas has been extended by Šitum *et al.*[22] from ABCDE to ABCDEFG, which is used in professional work and self-examinations. ABCDE have the same characteristic as above, followed by: F, feeling, itch, burn or pain; and G, growth, increasing size[22].

A combination of these signs and symptoms arouses suspicion of a melanoma. It would be desirable to use characteristics in a flier, with photographs for health education related to suspicion of melanomas.

Oral melanomas begin in the early phases as patchy brown or black blisters of irregular shape, which grow or develop into diffuse or nodular formations with focal points in hyper- and hypopigmentation, ulceration, bleeding, pain or loss of teeth (gingival location). Spotty or satellite lesions may appear around an OM, as on the skin[23-25]. They are a sign of already advanced melanoma, and are often accompanied by metastases to cervical lymph nodes. Melanomas of the oral cavity are located in 80% of cases on the mucosa of the palate and gingiva, and in other parts of the oral cavity, e.g., buccal mucosa, lips, tongue, base of the mouth, and uvula in 20% of cases[4,26,27]. From 35% to 37% of patients in whom OM develops, have pre-existing benign melanomatosis of the oral mucosa[28]. The presence of asymptomatic oral pigmentation at the site of an OM is on average discovered before diagnosis, in one-third of patients. These asymptomatic pigmentations may be the beginning of the radial phase of development of a tumor and are often unrecognized by the physician and patient. This phase may last for months or even years, until the signs of a tumor or tumor invasion appear. The absence of problems frequently causes patients to delay seeking medical care[29].

Differential Diagnosis of Oral Melanomas

Pigmentations of oral mucosa in terms of morphology may be solitary (focal), multiple or diffuse, and in terms of origin they are non-melanocytic and melanocytic[30]. Non-melanocytic pigmentations are tattoos, amalgam, medicament, heavy metals, lingua villosa nigra, and hemochromatosis. Melanocytic pigmentations are physiological (racial), ephelides (spots), smoker's melanosis, in systemic diseases, oral melanotic macule and palpable pigmented lesions (oral ma-lanoacanthoma, nevi – moles and oral malignant melanomas). Amelanotic oral melanomas are a particular problem, that is melanomas that occur *de novo*[29].

Methods in the Diagnosis of Melanomas

After a detailed family and personal history is taken, a very thorough clinical examination is conducted. Every pigmented change of the oral mucosa for which the precise cause is not known is suspect in terms of differential diagnosis for potential melanoma, and it must be diagnosed by histopathology. Histopathologic diagnosis is the gold standard in the diagnosis of melanomas.

Morphological examination of biopsy samples, stained using the standard hematoxylin-eosin (HE) method, is essential for setting the histopathologic diagnosis. The parameters evaluated by microscope include assessment of the following: presence of absence of melanocytes in the tumor (melanocytic or non-melanocytic tumor); cell morphology (epithelioid, spindle, plasmacytoid or mixed); form of cell organization (solid, alveolar, organoid or pagetoid); presence of necrosis, and perineural and perivascular invasion; and depth of tumor invasion, cell invasion according to the criteria of Prasad *et al.*[12] divided into: (a) noninvasive (*in situ*), (b) microinvasive (first level in which tumor cells are present in the superficial part of lamina propria), (c) invasive (second level with tumor cells in the lamina propria), and (d) deeply invasive (third level where the invasion extends into the muscle, bone or cartilage).

Oral melanoma is a relatively rare neoplasm with poor prognosis, and the non-melanocytic type has even worse prognosis, in view of the fact that it is biologically more aggressive and harder to diagnose, which makes treatment of lesions more often prolonged. Conventional morphological analysis in many cases is not sufficient, and it is complemented with some other techniques, such as histochemistry (e.g., Periodic Acid Schiff (PAS) and Fontana stains) and more recently immunohistochemistry (IHC). IHC is a diagnostic method that is today widely used in histopathology, in view of its diagnostic, prognostic, and recently also theranostic importance. IHC allows visualization of specific cell or tissue macromolecules from the globulin group (designated as immunoglobins, antigens or immunogens). The antigen-antibody reac-

tion, which is the basis of immunology, has found wide application in this method, which is performed *in situ* in human cells or tissues. The basis of this method is mutual affinity between antigens (epitope) and antibodies (paratope). The reaction is reversible because it is not based on the creation of chemical bonds. Visualization of the Ag-At bond is made using staining, that is, a chromogen, which does not change the biologic activity of the antibody. The most frequently used chromogen is 3,3'-diaminobenzedine (DAB) which stains the end product of the reaction brown, or 3-amino-9-ethylcarbazole which gives the end product of the reaction a red color.

Alongside IHC there is routine histopathologic diagnosis, molecular pathology methods are also used, which still cannot replace traditional morphological analysis, but can make significant contribution to correct establishment of the definitive histopathologic diagnosis.

Since OM cells may have an extremely polymorphic appearance (epithelioid, spindle or plasmocytoid) and this type of malignoma shows a wide morphological spectrum, and lesions may resemble epithelial, histologic, mesenchymal and neural tumors, the use of IHC in establishing definitive diagnosis is of great assistance. The most frequently used antibodies that react with melanocyte proteins are HMB-45, Melan A and protein S-100. HMB-45 is a 35-kDa glycoprotein melanosome and is a marker of activated melanocytes, so it is used in the diagnosis of melanomas. It is a very sensitive, but slightly less specific melanocyte marker, in view of the fact that it sometimes shows expression in some other cell types. It can show zonal intra-tumor variations in the intensity of staining.

The Melan-A protein is a product of the MART-1 gene and is specific for melanocyte cells, and thus also for the lesions which develop from them. It is also a less specific protein, in view of the fact that it is also found in some other cell types, that is, benign and malignant tumors of the adrenocortical region, tumors of the testicles with their origin in Leydig cells, as well as ovarian tumors originating from Sertoli and Leydig cells.

Protein S-100 is a 21-kDa protein of high sensitivity (97%-100%) and less specificity for melanocytes, since its expression is possible in lipocytes, chondrocytes, macrophages, and Langerhans and dendritic cells. Reduction in expression or loss of expression may

occur in the zones of melanoma with strong necrosis. Protein S-100, besides helping in determining tumor thickness, has been shown in some studies to be of a potential prognostic value, i.e. the intensity of staining by protein S-100 was in reverse correlation with the survival time[31-33].

All these routinely and most frequently used antibodies in the histopathologic diagnosis of OM are used in cases of melanocytic differentiation of tumor cells, i.e. in differentiating melanocytes from some other types of non-melanocytic malignant cells they resemble (e.g., cells of undifferentiated carcinomas, lymphomas), in visualization of occult tumor cells, assessment of the depth of tumor invasion, and in detection of metastasis. IHC is useful in the assessment of distribution-density, number and cytoarchitecture (degree of atypia) of the lines of the lesion.

Immunohistochemistry is not an absolutely sovereign diagnostic method; it is a very good auxiliary method, which is used abundantly in routine, especially in oncologic diagnosis. It cannot and must not replace traditional morphological diagnosis. IHC is an important but not obligatory diagnostic procedure. Immunohistochemical and molecular pathology methods are also used, which still cannot replace traditional morphological analysis, but can make significant contribution to correct establishment of the definitive histopathologic diagnosis.

In the diagnosis of OM, the following may also be used: computed tomography (CT); magnetic resonance imaging (MRI); and positron emission tomography (PET) which can hardly differentiate melanoma from nevus, but in combination of PET/CT it has diagnostic value[8].

Treatment of Melanomas

Treatment of OM primarily presumes surgical removal of the tumor, with or without neck dissection. That is to say, the region of the head is the anatomically most complex part of the human body, where in a small area there are vital organs, osteomuscular and blood vessel structures, and nerves, but no less important is to point out that in this region there is the most dense network of lymphatic vessels and the greatest number of lymph nodes. Due to the latter, the possibility of metastasis of melanoma localized on the head (and mucosa) is also greater than on the skin of the

body. Moreover, this fact is important in planning surgical procedure. It is no less important to point out that it is also a prominent localization, where the extent of the intervention involves mutilation and malformations that cannot be concealed. The skill of the surgeon, good planning of the procedure, and surgical technique are extremely important, not only for therapeutic reason, but also for the patient quality of life[34].

Treatment of OM consists of surgical removal of the tumor, with or without neck dissection.

Adjuvant therapy is also administered, which includes radiotherapy, chemotherapy, immunotherapy and immunomodulators[35].

Case Report 1

The patient B. E., a female aged 62, was admitted to the Clinical Department of Maxillofacial Surgery, Sarajevo University Hospital Centre, on April 16, 2007, due to tumorous changes in the region of the upper lip. The changes had been present for the previous 6 months as verrucous lesions and darker pigmentation, which were painless, with a tendency for gradual growth, and occasional spontaneous bleeding (Fig. 1). Her detailed medical history included no previous hospitalization, hereditary ailments, or allergies to food or medication. She took Lopril 1x5 mg as therapy and Apaurin when necessary. She was a nonsmoker, and did not consume alcohol. Clinical examination verified melanocytic changes localized on the mucosa, also affecting the angular part of the upper lip in the medial line, 2.5x2.5 cm in diameter, with regular edges,
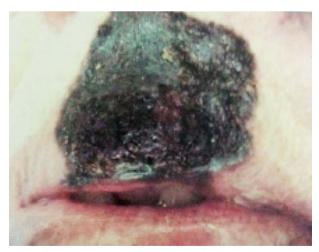
slightly raised above the level of the surrounding mucosa and skin. The regional lymph nodes were not palpable. Surgical excision of the changes and primary reconstruction of the defect using a localized flap was performed. The histopathology results indicated *Melanoma nodulare malignum mucosae labii superior* (Clark 4, Breslow 1.7 mm, T2b). After this, the patient was followed-up by the oncology consultant with regular examinations of the neck, abdomen and lung x-ray every six months.

In September 2011, due to bilateral neck lymphadenopathy, the patient was admitted to the hospital again. Bilateral supraomohyoid neck dissection was performed, and the histopathology results indicated regional dissemination of the disease. As part of the oncologic treatment, chemotherapy was administered (DTIC, dacarbazine), and the patient refused the proposed radiation treatment. The patient died on January 26, 2012.

Case Report 2

The patient M. A., a 59-year-old female, was admitted to the Clinical Department of Maxillofacial

Fig. 2. Clinical appearance of a tumor on the mucosa of the lower lip at the time of patient admission to the hospital.

Fig. 1. Mucosal melanoma of the upper lip.

Surgery, Sarajevo University Hospital Centre, on September 29, 2014, for extensive tumorous changes in the region of the lower lip. The changes had been present for several years as a small red nodule on the mucosa of the lower lip, with gradual growth (Fig. 2). The patient was a long-term neuropsychiatric patient with the diagnosis of schizophrenia. Her therapy included Haldol 2x2 mg, Trazem 1x1, Prazine 1x25 mg, and Apaurin when necessary. She denied any hereditary diseases. She had allergy to potatoes. She was a nonsmoker, and did not consume alcohol. Clinical examination verified a change of 5x5 cm in diameter, with nodular appearance, red color, covered with necrotic deposits, fixed by a narrower base to the red part of the lower lip and its mucosa, pulling the complete lower lip backwards. Surgical excision in the 'W' pattern was performed. The histopathology results indicated a nodular type malignant melanoma (Breslow c. 40 mm, Clark V, pT4b NxMx). At the time of histopathology report, the neck on the left side was clinically and by use of ultrasound positive. Cervical lymphadenectomy was performed on February 9, 2015, with supraomohyoid neck dissection on the right and radical neck dissection on the left side. The histopathology results showed the presence of metastatic lymph nodes in the left side of the neck and chronic reactive lymphadenitis on the right side of the neck. The patient was referred to oncology for conservative treatment according to the protocol for malignant melanomas. Currently, radiation treatment is under way.

Discussion

The incidence of cutaneous melanoma increased dramatically in the second half of the 20th century, in contrast to the incidence of melanomas of oral mucosa, which has remained stable. In a review article, Chang *et al.* analyzed 84,836 cases of melanoma (in the USA) recorded in the period from 1985 to 1994 and localized in the skin (91.2%), eyes (5.2%), mucosa (1.2%), and unknown primary localization (2.2%) (Table 1)[26]. In the study by Cheung *et al.*, there were 659 cases of melanoma of the gastrointestinal tract: 53.6% anorectal (anal 31.4%, and rectal 22.2%), 32.8% oropharyngeal, 5.9% esophageal, 2.7% of the stomach, 2.3% of the small intestine, 1.4% of the gallbladder, and 0.9% of the colon[27]. In the review article by Hicks and Flaitz, aggregated data are given from several articles related to

Table 1. Melanoma cases registered in the USA between 1985 and 1994

Localization	%	n
Skin	91.2	77,370
Mucosa	1.3	1,103
Head and neck	55.4	
Genital, women	18.0	
Anal/rectal	23.8	
Urinary	2.8	
Ocular	5.2	4,411
Uveal	85.0	
Conjunctival	4.8	
Other	10.2	
Unknown primary location	2.2	1,952
Regional metastasis	43.0	
Distant metastasis	57.0	

Table 2. Localization of 703 cases of melanoma of oral mucosa

Localization	n	%
Palate	223	32
Hard palate	66	9
Soft palate	7	1
Gingiva	37	5
Maxillary gingiva	114	16
Mandibular gingiva	50	7
Oral cavity	82	12
Buccal mucosa	46	6
Lips	45	6
Tongue	18	3
Base of the mouth	11	2
Uvula	4	<1

melanomas of the mucosa of the head and neck, which include 703 cases of oral mucosa and 770 cases of sinonasal mucosa (Table 2)[4,26,27]. In the review article by Mihajlović *et al.*[36], data are cited from the American literature that OM are rare tumors with an annual incidence of 0.2 *per* million, that is, 1 case *per* 5 million people[37]. The authors from South America provide a figure of 1.2 OM cases *per* 10 million[38]. OMs are more common in the Japanese population, accounting for 7.5% of all melanomas. Skin melanomas in Japan have a lower incidence than in the USA[17,39].

In the Republic of Croatia, no separate records are kept of melanomas of the oral mucosa[40]. In the Federation of Bosnia and Herzegovina, no records are kept of melanomas of the oral mucosa either, but records are kept of topographic diagnoses of oral carcinomas of the lips, tongue, mouth, salivary glands, tonsils and oropharynx[41].

The prognosis of OM is poor, the 5-year survival is between 10% and 25%, and the average survival is less than 2 years. For example, the 5-year survival in patients with positive cervical lymph nodes is 16.4% and in patients with negative cervical lymph node findings 38.7%[8]. OM more often affects men than women (2:1). In men, it occurs one decade earlier than in women. In men, it occurs most often in the decade from 51 to 60 years of age, and in women between 61 and 70 years of age[8].

Conclusion

Primary melanomas of the oral mucosa are a very rare and aggressive malignancy. OM occurs from the existing melanin pigmentation, but some develop *de novo*. Dentists and family physicians, when examining pigmented oral mucosal lesions, should suspect OM in their differential diagnosis. Therefore, in every patient with oral pigmentation, oral biopsy specimen should be obtained as a diagnosis based solely on clinical appearance may be insufficient. Histopathologic diagnosis is the gold standard in the diagnosis of melanomas. About 80% of OMs are located in the region of the mucosa of the palate and maxillary gingiva.

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Sažetak

MELANOM ORALNIH SLUZNICA – DVA PRIKAZA SLUČAJA I PREGLED LITERATURE

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Oralni melanom (OM) nastaje iz aktiviranih ili genski izmijenjenih epidermnih melanocita. Nema znanstvenih dokaza da se OM može vezati za fizikalne, kemijske i termičke iritacije ili druge rizične čimbenike usne šupljine. Prema podacima iz različitih zemalja na OM otpada od 0,2% do 7,5% (Japan) svih slučajeva melanoma kože i sluznica. Odnos muškaraca i žena za OM je 2:1. Oko 80% slučajeva OM locirano je na sluznici tvrdog nepca i maksilarne gingive. U ovom radu prikazuju se dva slučaja OM gornje i donje usne u osoba ženskog spola u dobi od 62 i 59 godina. Opisane su dijagnoza, diferencijalna dijagnoza i terapija.

Ključne riječi: *Melanom – patologija; Oralni tumori – dijagnostika; Oralni tumori – terapija; Prikazi slučaja*