

Malignant Melanoma of the Oral Cavity

M.S. Hashemi Pour¹✉

¹Assistant Professor, Department of Oral Medicine, Faculty of Dentistry, Kerman University of Medical Sciences, Kerman, Iran

Abstract:

Oral malignant melanoma (OMM) accounts for 5% of all oral malignancies. It is a rare aggressive neoplasm usually found on the hard palate and gingiva. The etiology is unknown, but tobacco and chronic irritation are suggested as probable causative factors. Over 30% of the cases have been reported to arise from pre-existing pigmented lesions. A biopsy is required to establish the diagnosis and the treatment of choice is surgery which may be affected by several factors such as size of the lesion and anatomic location. Despite aggressive resection and adjuvant treatments such as chemotherapy and immunotherapy, the five-year survival rate of this malignancy is poor.

Key Words: Melanoma; Oral mucosa; Oral Cavity

Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2007; Vol: 4, No1)

✉ Corresponding author:
MS Hashemi Pour, Department
of Oral medicine, Faculty of
Dentistry, Kerman University
of Medical Sciences, Shafa St.,
Kerman, Iran
m_s_hashemipour@yahoo.com

Received: 25 April 2006
Accepted: 6 September 2006

INTRODUCTION

Melanocytes are neural crest-derived cells that migrate to the skin, mucous membranes and several other sites. In the skin, they provide protection from ultraviolet radiation and sun exposure. The function of melanocytes in the mucosa is not fully understood, but their presence along the tips and peripheries of the rete ridges is well established. Variation in the density of melanocytes is seen in different parts of the body and mucosal epithelia, for example, the ratio of melanocytes to basal keratinocytes in the gingiva is 1 to 15. The cytologic appearance, organization and biologic characteristics of melanocytes, nevus cells and melanoma cells are considerably different. Melanoma cells are round to spindle shaped and may demonstrate some features of nevus cells such as lack of dendritic processes and loss of contact inhibition. These malignant cells are pleomorphic, with large, irregular hyperchromatic nuclei, prominent nucleoli, and conspicuous mitotic activity [1].

The incidence of melanoma has been steadily

increasing in the past several decades with an annual increase of 3 to 8%, worldwide. The life-time risk of the development of an invasive melanoma in the United States was only 1 in 500 in 1935, while 1 in 600 in 1960; 1 in 105 in 1992 and 1 in 88 in 1996. The life-time risk is estimated to be 1 in 75, by the year 2000 [2].

Melanoma infrequently arises from mucosal surfaces most commonly the head and neck (typically involving the nasal and oral cavity); vulva; and anorectal mucosa [2,3]. Head and neck mucosal melanomas are much less common than their cutaneous counterparts and probably represent less than 1-8% of all melanomas [3-11].

Epidemiology

The exact incidence rate of oral melanoma is not available. However, they are rare and estimated to represent 1-2% of all oral malignancies [1,3-18] and account for about 0.2% to 8% of all melanomas [19,20]. Oral melanoma is more common in countries like Japan,

Uganda and India [3,6,10,11,14,21]. Among Japanese people, OMM comprises 11-14% of all melanomas [4,6,10] but is rare in Australia [8]. Mucosal malignant melanoma seems to be more common in Eastern as compared to Western countries [10]. Primary oral melanomas are extremely rare in the United States and account for less than 2% of all melanomas. At 1.2 cases per 10 million people per year, the annual incidence of oral melanoma is very low [22].

According to a recent investigation in Africa, 1.7% of all melanomas in Sudan occurred in the oropharynx and 0.9% of the melanomas in Nigeria were found in the oral cavity. The mouth was suggested as a common site for melanoma in Uganda, with a frequency of 8% in 125 melanomas. This was reported as 4.6% in a similar study with a slightly larger sample size [14, 17].

Jackson and Simpson [23] indicated that primary malignant melanoma of the oral cavity represented less than 2% of all malignant melanomas. Robertson et al [9] and Reddy et al. [10] demonstrated that primary malignant melanoma of the oral cavity comprised 0.4% to 1.3% of all malignant melanomas. van der Waal et al [8] showed that only 2.5% of all melanomas were primary malignancies of the oral cavity. Subsequent studies have confirmed the predominance of oral melanoma in the American Caribbean, African and Indian populations. According to studies from India, between 20.41 and 34.4% of all melanomas occurred in mucosal surfaces and up to 16% of these tumors were intraoral [10].

Oral melanoma is very uncommon at any site in prepubertal children of all races [14,18]. This malignancy is a lesion of adulthood, rarely identified under the age of 20 years. In various studies the highest incidence of malignant melanoma is reported in the fifth decade of life (40-70 years) [3-6,8,9,15,16,18, 23-26]. Barker et al [27] showed that the average age of patients with mucosal melano-

ma was 56 years with an age range of 22 to 83 years.

Males appear to be more often affected with OMM than females [1,3,7-10,12,14-16,23,25, 27-29]. In different studies the male to female ratio ranged from 1/1 to 2/1 [3,8,9,15,16,30]. Barker et al [8] showed a gender distribution of 37 males to 13 females (ratio = 2.8) [27]. In the Netherlands, oral malignant melanomas were slightly more common in men. In their review of the literature, Hicks and Flaitz [1] described a male predilection and an age range of 22 to 83 years, with a mean age of 56 years. Hashemipour also reported a male predominance (male to female ratio 2/1) and a mean age of 69.2 year (range, 56 to 77 years) in Kerman province, Iran [31].

Morris and Horn [14] found that malignant melanomas were 4.4 times more common in whites than Negroes. Reports of cases of oral melanomas in blacks are infrequent.

Primary melanoma often occurs in the hard palate and maxillary gingiva. Other oral sites include the mandible, tongue, buccal mucosa and upper and lower lips [1,3-5,7-10,12,15,17, 21,23,25,27,29,30,32,33,34].

Ethnic groups commonly affected by oral melanomas are Japanese, Native Americans, and Hispanics [35].

Etiology

In contrast to cutaneous melanomas, the pathogenesis and etiology of mucosal melanoma are still unclear. Sun exposure and tendency to tan are not an issue in oral melanomas, yet other factors like family history, various syndromes and cytogenetic defects have not been extensively investigated in these neoplasms. The rarity of this malignancy could also be responsible for the lack of information in different countries [1,12,27,36].

There appears to be no geographic difference and possibly only slight ethnic and gender variations in the risk factors of oral melanoma [7].

Like their cutaneous counterparts, primary oral melanomas are believed to arise either *denovo* (30% of cases) or from nevi and pre-existing pigmented areas [1-3,5,6,8,12,15,18,23,37].

Fair complexion and light hair, a tendency to sunburn easily, a history of painful or blistering sunburns in childhood, indoor occupations with outdoor hobbies, a personal history of melanoma or dysplastic or congenital nevus (xeroderma pigmentosum and basal cell nevus syndrome) have been implicated as etiologic- or risk-factors in melanoma of the skin, but not in the oral cavity. Some of the oral melanomas are believed to originate from junctional nevi. Also on rare occasions, oral melanomas have been reported to arise from pre-existing Hutchinson's malignant lentigo, which occurs occasionally in the oral mucosa [5,6].

Mechanical traumas including injury from ill-fitting prostheses and infection have been cited as possible causative factors for melanomas of the mouth, but there is no real proof for their etiologic role [2,14].

It has been suggested that oral habits and self-medication may be of etiologic significance in some Indian and African populations [2,14]. Racial pigmentation probably bears a negative relationship to melanoma [9].

Clinical Features

According to Tanaka et al, oral melanomas could be classified into five types, based on their clinical appearance: pigmented nodular, nonpigmented nodular, pigmented macular, pigmented mixed and nonpigmented mixed [38]. This neoplasm may occur with or without a radial growth phase [2]. The clinical coloration of oral melanomas has a wide range, which can appear as black, gray, purple, and even reddish. While some lesions are uniform in color, others exhibit marked variations. The tumors are asymmetric, irregular in outline, and occasionally multiple. Their surface architecture ranges from macular to ulcerated and nodular [4,5,7,15]. Unpredictable and

widespread metastasis is a well known feature of malignant melanoma. Distant spread to bone, most often the vertebrae, is encountered in end-stage patients. Lymph nodes, central nervous system, lungs and liver are also common regions for metastasis. The oral mucosa is a rare site but soft tissues, especially the tongue may be involved by metastatic melanoma [2].

Few symptoms are found early in the course of this malignancy. The patients' attention may be drawn to the lesion by detection of a swelling, especially in a pigmented area. The tumor may also cause hemorrhage and loosening of teeth or it might interfere with proper fitness of a denture. Pain is an uncommon symptom of malignant melanoma and is generally found only in more advanced cases [3,5,8,23,25,27]. This tumor can cause extensive destruction of the underlying bone in 78% of the patients [5]. Some oral melanomas are amelanotic and appear clear on clinical examination. Amelanotic oral malignant melanoma (AOMM) is a rare tumor that is difficult to diagnose [39]. In two different studies, less than 10% of oral melanomas were described as amelanotic [1,27].

Histological Features

The presence of atypical melanocytes in the epithelial-subepithelial junction and an increased number of these cells in the biopsy of oral melanotic lesions are considered to be suspicious signs for malignant melanoma [6,40,41]. In most instances, the melanoma cells contain melanin pigmentation, but they may be deficient in melanin (amelanotic melanoma). Considering that melanomas can mimic a variety of undifferentiated tumors, a lack of production of this pigment may cause diagnostic confusion at the light microscopic level. Immunoreactivity of the lesional cells to antibodies against S-100, MART-1, and HMB-45 can be beneficial in distinguishing these lesions from other malignancies [6].

An unusual feature reported to occur in a number of mucosal melanomas is pseudo-carcinomatous hyperplasia of the overlying epithelium, which has also been described in association with other melanotic lesions, like Spitz nevi [40]. This feature may cause confusion with the commonly-encountered oral squamous cell carcinoma and should be taken into consideration during histopathologic evaluation of a biopsy.

Diagnosis

Diagnosis of oral mucosal melanomas may be difficult for several reasons such as small biopsy size, unrepresentative sampling, biopsy of late-stage lesions with indistinct epithelial-stromal interface, lack of clinical data and the inability of the clinician and/or pathologist to detect early in situ lesions [7]. Because of the frequent delay in the diagnosis of oral melanomas, they are usually deeper at the time of diagnosis as compared to their cutaneous counterparts [24]. This may be responsible for the poor five-year survival (15% to 38%) reported in these tumors. In addition bone invasion and the rich vascular supply of the oral cavity could contribute to the dissemination of melanomas [2,42,43].

The "ABCD" system of evaluation is used to differentiate malignant melanoma from benign pigmented lesions. These features are as follow:

A, Asymmetry; B, Border irregularity frequently including a notch or irregular indentation; C, Color variegations such as red, white, and blue; and D, Diameter greater than 0.6 mm. Regarding the different colors in melanoma, shades of blue are considered to be the most ominous. White, pink, and gray shades have been related to the ability of melanomas to undergo spontaneous regression, while red and pinks are suggested to reflect inflammation [25].

Three criteria have been proposed by Greene et al [44] that can be helpful in the diagnosis of

primary oral melanoma. These include presence of malignant melanoma in the oral mucosa; the exclusion of melanoma at any other primary site; and histopathologic observation of "junctional activity" which is described as melanocytes arranged along the basal layer of the surface epithelium [44].

According to Tanaka et al [42], the biologic behavior of melanoma may be associated with the expression of Rb, pRb2/p130, p53 and p16 proteins and they may be helpful in the prediction of the outcome of this neoplasm.

Regional metastases to the submandibular and cervical lymph nodes should be evaluated by CT and MRIs [4]. It has been suggested that a general practitioner should not perform a biopsy on a pigmented lesion, since there is a reasonable chance that it may be a malignant melanoma [45]. In addition considering the fact that some investigators believe that cutting a malignant neoplasm during incisional biopsy could result in seeding of the lesional cells into the adjacent tissues or even the blood and lymphatics, the decision of whether or not to biopsy a pigmented lesion would be extremely difficult [46].

The relatively high incidence of malignant versus benign melanotic lesions suggests that they should be assessed with special care [3].

Differential Diagnosis

The differential diagnosis for OMM includes oral melanotic macule, smoking-associated melanosis, medication induced melanosis (antimalarials drugs and Minocycline), melanoplakia, pituitary-based Cushing's syndrome, post-inflammatory pigmentation, melanoacanthoma, melanocytic nevi of the oral mucosa, blue nevi, Spitz nevi, Addison's disease, Peutz-Jeghers syndrome, amalgam tattoo, Kaposi's sarcoma, physiologic pigmentation, pigmentation related with the use of heavy metals, and many other conditions sharing some macroscopic characteristics with OMM [41,43,47].

This neoplasm should also be differentiated

from other malignant entities, such as poorly-differentiated carcinoma and large cell anaplastic lymphoma [41].

It has been stated that epulis or squamous cell carcinomas should be considered in the clinical differential diagnosis of amelanotic malignant melanomas when they are encountered in a vertical growth phase, without radial growth [39].

Management

Surgery is the mainstay of treatment, but can be difficult due to anatomic restraints. Although melanoma is classically not radio-sensitive, occasional patients have shown a good response to radiation therapy especially in early or in situ melanomas. Other treatment modalities are similar to those used for cutaneous melanoma. Immunotherapy has been successfully used but chemotherapy has demonstrated a relatively low response rate [4-6,8,9,13,17,21,24, 25,26,32,36,37].

Dacarbazine-DTIC, $INF\gamma$ and $INF\text{-}\alpha\text{-}2b$ have been described as chemotherapeutical and immunotherapeutical treatments, associated with Bacillus Calmette-Guerin vaccine and recombinant interleukin-2 (rIL-2), in different combinations [48].

Prognosis and Survival

Most melanomas of the oral cavity are large at presentation and have a poorer prognosis than cutaneous melanomas [3,6,7,12,13,16-18,25,37,49].

Clark's and Breslow's classifications are the most widely used systems for evaluation of the prognosis of skin melanomas. The former assesses depth of invasion, whereas Breslow's system measures tumor thickness from the greatest depth of the neoplasm to the top of the granular cell layer. The risk for developing metastatic lesions from primary cutaneous melanomas increases with tumor thickness [6]. These two grading systems have not been validated as prognostic predictors in oral

melanomas probably owing to the rarity of this lesion. Additionally, histologic landmarks comparable to skin layers, e.g. reticular and papillary dermis, have not been demonstrated in the oral mucosa [50].

Furthermore, in contrast to cutaneous melanomas, most oral melanomas are larger than 4mm at the time of initial presentation. This factor, together with inadequate resection of margins and higher stage at initial diagnosis, may contribute to the discrepancy in the patients' 5-year survival rates between cutaneous (80%) and oral melanomas (15%) [1]. Survival rates are generally poorer for patients with regional or distant metastasis [23].

It has been reported that the average life expectancy from the initial diagnosis of OMM is about 18 months. According to Sampat and Sirsates [5], 79% of patients might die within 5 years of diagnosis. Vairaktaris et al [51] also showed that the 5-year survival rate of intraoral melanoma does not exceed 5-9%.

A three-level microstaging system has been proposed by Prasad et al. Accordingly, Level I was defined as melanoma in situ without evidence of invasion or with the presence of invasive individual or clusters of less than 10 atypical melanocytes near the epithelial-subepithelial junction. Level II tumors consisted of melanoma cells limited to the lamina propria, and Level III was described as invasion into deep connective tissue, including skeletal muscle, bone, or cartilage. The microstaging system was found to be a prognostically significant factor in patients with localized, lymph node-negative, Stage I head and neck malignant melanoma [52].

Melanomas with a high clinical stage at presentation, a thickness of greater than 5mm, vascular invasion, absence of melanosis and nodal and/or distant metastases are considered to carry a worse prognosis than those that lack these features [5,6,8].

The 5-year survival rate for OMM has been reported to be 15% with a median survival of

25 months. The 5-year survival rate for palatal and gingival melanomas was found to be 22 and 46 months, respectively. This reveals a better prognosis for palatal as compared to gingival melanomas [1]. Recurrences may occur up to 10-15 years after initial treatment [2].

CONCLUSIONS

Malignant melanomas of the oral cavity are different from cutaneous melanomas; therefore establishing new criteria for the diagnosis and treatment of this malignancy should be considered. Dentists and doctors who treat oral lesions should be aware of the necessity for early diagnosis of melanoma.

REFERENCES

- 1- Hicks MJ, Flaitz CM. Oral mucosal melanoma: epidemiology and pathobiology. *Oral Oncol* 2000 Mar;36(2):152-69.
- 2- Freedberg IM, Wolff K, Austen KF, et al. *Dermatology in general medicine*. 5th ed, United States: Mc Graw-Hill; 1999:981,1097.
- 3- Steidler NE, Reade PC, Radden BG. Malignant melanoma of the oral mucosa. *J Oral Maxillofac Surg* 1984 May;42(5):333-6.
- 4- Greenberg MS, Glick KM. *Burket's Oral Medicine*. 9th ed, Hamilton: BC Decker; 2003: 131-132, 214-215.
- 5- Prabhu SR, Wilson DF, Daftary DK. *Oral diseases in the Tropics*. New York: Oxford University Press; 1992: 460-1.
- 6- Neville BW, Damm D, Allenc R, Bouquot JE. *Oral and Maxillofacial Pathology*. 2nd ed. Philadelphia: W.B Saunders; 2002:334,376-380.
- 7- Silverman S. *Oral cancer*. 5th ed. Hamilton. London: BC Decker Inc; 2003:155-7.
- 8- van der Waal RI, Snow GB, Karim AB, van der Waal I. Primary malignant melanoma of the oral cavity: a review of eight cases. *Br Dent J* 1994 Mar 5;176(5):185-8.
- 9- Robertson GR, DeFiebre BK, Firtell DN. Primary malignant melanoma of the mouth. *J Oral Surg* 1979 May;37(5):349-52.
- 10- Reddy CR, Rao TR, Ramulu C. Primary malignant melanoma of the hard palate. *J Oral Surg* 1976 Oct;34(10):937-9.
- 11- Gu GM, Epstein JB, Morton TH. Intraoral melanoma: long-term follow-up and implication for dental clinicians. A case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003 Oct;96(4):404-13.
- 12- Bina S. Primary malignant melanoma of the oral cavity in Iranians (review of 18 cases). *J Oral Med* 1979 Apr-Jun;34(2):51-2.
- 13- Rapidis AD, Apostolidis C, Vilos G, Valsamis S. Primary malignant melanoma of the oral mucosa. *J Oral Maxillofac Surg* 2003 Oct;61(10): 1132-9.
- 14- Goubran GF, Adekeye EO, Edwards MB. Melanoma of the face and mouth in Nigeria. A review and comment on three cases. *Int J Oral Surg* 1978 Oct;7(5):453-62.
- 15- Bennett AJ, Solomon MP, Jarrett W. Superficial spreading melanoma of the buccal mucosa: report of case. *J Oral Surg* 1976;34(12):1109-11.
- 16- Gorsky M, Epstein JB. Melanoma arising from the mucosal surfaces of the head and neck. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998 Dec;86(6):715-9.
- 17- Cebrián Carretero JL, Chamorro Pons M, Montesdeoca N. Melanoma of the oral cavity. Review of the literature. *Med Oral* 2001 Nov-Dec;6(5):371-5.
- 18- Shah JP. *Cancer of Head and Neck*. Hamilton: BC Decker Inc; 2001:40-42, 79-80
- 19- Garzino Demo P, Carbon M, Carrozzo M, Brocchettoletti R, Gandolfo S. Melanoma of the oral cavity. Review of the literature. *Minerva Stomatol* 1997 Jun;46(6):329-35.
- 20- Rapini RP, Golitz LE, Greer RO, Krekorian EA, Poulson T. Primary malignant melanoma of the oral cavity. A review of 177 cases. *Cancer* 1985 Apr 1;55(7):1543-51.
- 21- Lopez-Graniel CM, Ochoa-Carrillo FJ, Meneses-García A. Malignant melanoma of the oral cavity: diagnosis and treatment experience in a Mexican population. *Oral Oncol* 1999 Jul;35(4): 425-30.

- 22- D'Silva NJ, Kurago Z, Polverini PJ, Hanks CT, Paulino AF. Malignant melanoma of the oral mucosa in a 17-year-old adolescent girl. *Arch Pathol Lab Med* 2002 Sep;126(9):1110-3.
- 23- Jackson D, Simpson HE. Primary malignant melanoma of the oral cavity. *Oral Surg Oral Med Oral Pathol* 1975 Apr;39(4):553-9.
- 24- Rapini RP. Oral melanoma: diagnosis and treatment. *Semin Cutan Med Surg* 1997 Dec;16(4):320-2.
- 25- Wood NK, Goaz PW. Differential diagnosis of oral and maxillofacial lesions, 5thed. United States: Mosby; 1997: 67-68, 190.
- 26- Liebross RH, Morrison WH, Garden AS, Ang KK. 50 Mucosal melanoma of the head and neck. *Inter J Radiat Oncol* 1997;39(2):159.
- 27- Barker BF, Carpenter WM, Daniels TE, Kahn MA, Leider AS, Lozada-Nur F, et al. Oral mucosal melanomas: the WESTOP Banff workshop proceedings. Western Society of Teachers of Oral Pathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997 Jun;83(6):672-9.
- 28- Harrison LB, Session RB, Hong WK. Head and Neck Cancer. Philadelphia: Lippincott-Raven; 1999: 309, 320, 326-328, 721-724.
- 29- Daley T, Darling M. Nonsquamous cell malignant tumours of the oral cavity: an overview. *J Can Dent Assoc* 2003 Oct;69(9):577-82.
- 30- Patel SG, Prasad ML, Escrig M, Singh B, Shaha AR, Kraus DH, et al. Primary mucosal malignant melanoma of the head and neck. *Head Neck* 2002 Mar;24(3):247-57.
- 31- Hashemipour MA, Zarei MR, Chamani G. Epidemiological aspects of non- squamous cell malignant tumors of the oral cavity in Kerman province(1991-2002). Doctorate Thesis. 2004 July. School of dentistry. Kerman University of Medical Sciences.
- 32- Doval DC, Rao CR, Saitha KS, Vigayakumar M, Misra S, Mani K, et al. Malignant melanoma of the oral cavity: report of 14 cases from a regional cancer centre. *Eur J Surg Oncol* 1996;22(3):245-9.
- 33- Zarei MR, Chamani G, Hashemipour MA. Epidemiological aspects of non- squamous cell malignant tumors of the oral cavity in Iranian. Abstract of the article in the 10th international congress on the oral cancer April 2005; Island of Crete. Greece.
- 34- Zarei MR, Chamani G, Hashemipour MA. Epidemiological aspects of non- squamous cell malignant tumors of the oral cavity in Iranian. *J Dent TUMS* 2007;(under publication)
- 35- Tremblay JF, O'Brien EA, Chauvin PJ. Melanoma in situ of the oral mucosa in an adolescent with dysplastic nevus syndrome. *J Am Acad Dermatol* 2000 May;42(5 Pt 1):844-6.
- 36- Nandapalan V, Roland NJ, Helliwell TR, Williams EM, Hamilton JW, Jones AS. Mucosal melanoma of the head and neck. *Clin Otolaryngol Allied Sci* 1998 Apr;23(2):107-16.
- 37- Ord RA, Blanchaert RH. Oral Cancer. Chicago: Quintessence; 1999: 75-76.
- 38- Tanaka N, Amagasa T, Iwaki H, Shioda S, Takeda M, Ohashi K, Reck SF. Oral malignant melanoma in Japan. *Oral Surg Oral Med Oral Pathol* 1994 Jul;78(1):81-90.
- 39- Tanaka N, Mimura M, Kimijima Y, Amagasa T. Clinical investigation of amelanotic malignant melanoma in the oral region. *J Oral Maxillofac Surg* 2004 Aug;62(8):933-7.
- 40- Kamino H, Tam ST, Alvarez L. Malignant melanoma with pseudocarcinomatous hyperplasia- an entity that can simulate squamous cell carcinoma. A light-microscopic and immunohistochemical study of four cases. *Am J Dermatopathol* 1990 Oct;12(5):446-51.
- 41- González-García R, Naval-Gías L, Martos PL, Nam-Cha SH, Rodríguez-Campo FJ, Muñoz-Guerra MF, et al. Melanoma of the oral mucosa. Clinical cases and review of the literature. *Med Oral Patol Oral Cir Bucal* 2005;10(3):264-71.
- 42- Tanaka N, Odajima T, Mimura M, Ogi K, Dehari H, Kimijima Y, et al. Expression of Rb, pRb2/p130, p53, and p16 proteins in malignant melanoma of oral mucosa. *Oral Oncol* 2001 Apr;37(3):308-14.
- 43- Eisen D, Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity. *J Am Acad Dermatol* 1991 Apr;24(4):527-37.
- 44- Greene GW, Haynes JW, Dozier M, Blumberg

- JM, Bernier JL. Primary malignant melanoma of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 1953;6(12):1435-43.
- 45- Reichart PA, Philipsen HP. *Color Atlas of Dental Medicine*. 1st edition, Thieme, 2000 p: 16.
- 46- Meleti M, René Leemans C, Mooi WJ, Vescovi P, van der Waal I. Oral malignant melanoma: a review of the literature. *Oral Oncol* 2007 Feb;43(2):116-21. Epub 2006 Aug 23.
- 47- Symvoulakis EK, Kyrmizakis DE, Drivas EI, Koutsopoulos AV, Malandrakis SG, Skoulakis CE, et al. Oral mucosal melanoma: a malignant trap. *Head Face Med* 2006 Mar 28;2:7.
- 48- Takagi M, Ishikawa G, Mori W. Primary malignant melanoma of the oral cavity in Japan. With special reference to mucosal melanosis. *Cancer* 1974 Aug;34(2):358-70.
- 49- Gérard E, Fidanza JP, Lopez-Melon E, Truchetet F. Malignant melanoma of the oral mucosa. *Actual Odontostomatol (Paris)* 1991 Jun;45(174):237-46. French.
- 50- Marco Meleti, Wolter J. Mooi and Isaïc van der Waal. Oral malignant melanoma associated with pseudoepitheliomatous hyper-plasia. Report of a case. *J Cutan Pathol* 2006;33:331-3.
- 51- Vairaktaris E, Iatrou I, Ragos V, Petraki K, Martis C. Primary melanoma of the oral cavity Hell Period *Stomat Gnathopathoprosopike Cheir* 1989 Mar;4(1):31-6.
- 52- 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;100(8):18.