The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (8), Page 3016-3020

Natural History and Surgical Management of Oral Malignant Melanoma

Rahmah Hameed Al Salman [1] , Mohammed Essam Fageha [2] , Khalid Abdulrahman S Alghamdi [3] , Suzan Sulaiman hamad Shamlan [4] , Yara Tareq Mohammed Talab [4] , Alaa Omar D Almalki [3] , Wajdi Mohammed Bardisi 5 , Khaled Hamad M Albaradi [6] , Majid Gais Faisal Alsharif [7]

1- Alfarabi College , 2- Al-Farabi College for Nursing and Dentistry , 3- Jordan university of Science and technology , 4- 5th years general dentist on batterjee medical college , 5- umm al-qura university faculty of dentistry , 6- Intern in KAU , 7- Batterjee medical college

ABSTRACT

Pigmented entities are relatively common in the oral mucosa and arise from intrinsic and extrinsic sources. Conditions such as melanotic macules, nevi, smoker's melanosis, amalgam and graphite tattoos, racial pigmentation, and vascular blood-related pigments occur with some frequency. Addison disease, Peutz-Jeghers syndrome, and Laugier-Hunziker syndrome also appear in perioral and oral locations as pigmented macules. Detailed knowledge of melanoma at the molecular level allows the development of new treatment alternatives and to design effective new drugs. Addison disease presents as adrenal cortical hypofunction along with splotchy or generalized bronzing of the mucosa and skin. Peutz-Jeghers syndrome has periorificial freckling along with hamartomatous intestinal polyps, and, as a differential diagnosis, Laugier-Hunziker syndrome presents with macular mucocutaneous hyperpigmentation and melanonychia with no known systemic disease association. We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1, 1970, through February 28, 2017.

Keywords: Malignant Melanoma, Oral Mucosa, Immunotherapy.

INTRODUCTION

Pigmented entities are relatively common in the oral mucosa and arise from intrinsic and extrinsic sources. Conditions such as melanotic macules, nevi, smoker's melanosis, amalgam and graphite tattoos, racial pigmentation, and vascular blood-related pigments occur with some frequency. The incidence of melanoma is increasing worldwide. Melanomas represent 3% of all skin cancers but 65% of skin cancer death [1]. Melanoma is currently the fifth and sixth most common solid malignancy diagnosed in men and women, respectively [2]. The rates of melanoma have been rising for at least 30 years [3]. Although melanoma is no longer considered just ‘one disease’, pathologists will continue to have important role in identifying and describing tumor subtypes [4].

More detailed understanding of melanoma allows the development of new specific treatment alternatives, which are targeted at specific receptors or the genes of tumor cells. Addison disease, Peutz-Jeghers syndrome, and Laugier-Hunziker syndrome also appear in perioral and oral locations as pigmented macules. Addison disease presents as adrenal cortical hypofunction along with splotchy or generalized bronzing of the mucosa and skin. Peutz-Jeghers syndrome has periorificial freckling along with hamartomatous intestinal polyps, and, as a differential diagnosis, Laugier-Hunziker syndrome presents with macular mucocutaneous hyperpigmentation and melanonychia with no known systemic disease association. Oral pigmentations may range from light brown to blue-black, red, or purple. The color depends on the source of the pigment and the depth of the pigment from which the color is derived. Melanin is brown, yet it imparts a blue, green, or brown color to the eye.

This effect is due to the depth and density of the pigmented cells (or melanin granule dispersion) and the physical properties of light absorption and reflection described by the Tyndall light phenomenon or effect. Oral conditions with increased melanin pigmentation are common; though, melanocytic hyperplasias or hamartomas are rare. Clinicians should visually examine the oral cavity, obtain good clinical histories, and be willing to perform a biopsy on any pigmented condition that is not readily explainable or diagnosed. Patients with oral malignant melanoma regularly recall having an existing oral pigmentation month to years before diagnosis, and the condition may even have elicited prior comment from examining physicians and dentists (or healthcare providers, when considering the auxiliaries).

In contrast to the incidence of cutaneous melanoma, which continues to rise, the incidence of oral melanoma has remained stable for more

Received: 3/9/2017 DOI: 10.12816/0042849
Accepted: 13/9/2017

than 30 years. Surveillance data in the United States are not available for oral melanoma alone. Data for oral melanoma are included in the combined statistics for oral cancer. In a review of the large studies, melanoma of the oral cavity is reported to account for 0.2-8% of melanomas and approximately 1.6% of all malignancies of the head and neck [5]. In several studies, primary lesions of the lip and nasal cavity correspondingly are included in the statistics, thus increasing the frequency.

A critical review of the literature by Hicks and Flaitz found that the vast majority of melanomas occur on the skin (91.2%); ocular melanomas account for 5.3%, unknown primary lesions account for 2.2%, and melanomas of the mucous membrane account for 1.3% [6]. The oral mucosa is primarily involved in less than 1% of melanomas, and the most common locations are the hard palate and maxillary gingiva. Metastatic melanoma most frequently affects the mandible, tongue, and buccal mucosa. Internationally, oral melanoma is more common in the Japanese than in other groups. This observation is based on a review of frequently cited historical literature. Oral malignant melanoma, although rare in white persons, remains a major cause for concern. In Japan, oral melanomas account for 11-12.4% of all melanomas, and males may be affected slightly more often than females [7]. This percentage is higher than the 0.2-8% reported in the United States and Europe. Since cutaneous melanoma is less common in more darkly pigmented races, people of these races have a greater relative incidence of oral mucosal melanoma [8].

The rarity of oral melanoma has led to uncertainty in defining gender predilections, as some studies have specified a decided male predilection while others have shown a slight female predilection [9, 10]. A roughly equal gender distribution of melanoma in the skin occurs. In Japan, data suggest an equal or slight male predilection.

The study was done according to the ethical board of Umm Al Qura university.

Staging of malignant melanoma

The American Joint Committee on Cancer (AJCC) does not have published guidelines for the staging of oral malignant melanomas. Most practitioners use general clinical stages in the assessment of oral mucosal melanoma. Lesions thinner than 0.75 mm rarely metastasize, but they do have the potential to do so. On occasion, a small primary lesion is discovered after a symptomatic lymph node is harvested.

Table 1: General clinical stages in the assessment of oral mucosal melanoma

Stage	Assessment of oral mucosal melanoma
Stage I	Localized disease
Stage II	Regional lymph node metastasis
Stage III	Distant metastasis

Prasad et al [11] and Patel et al [12] proposed microstaging for lymph node–negative tumors (Table 2). Median survival declines with each increasing level of invasion.

Table 2: Micro staging for lymph node–negative tumors

Stage	Microstaging for lymph node–negative tumors
Stage I	Melanoma in situ (noninvasive)
Stage II	Invasion of the lamina propria only
Stage III	Invasion of deeper tissues (skeletal muscle, bone, or cartilage)

DIAGNOSIS

Tissue biopsy is the only study that is effective in diagnosing oral malignant melanoma. Perform clinical examination, and biopsy suspicious, unexplained lesions. Diseases and pigmented entities that should be considered when evaluating a patient with suspected oral malignant melanoma include the following:

Table 3: Diagnosis of oral mucosal melanoma

Diseases and pigmented entities	Other conditions
Addison Disease	Amalgam or graphite tattoo
Blue Nevi	Melanocytoma
Ephelides (Freckles)	Oral melanotic macule
Dermatological Manifestations of Kaposi Sarcoma	Peutz-Jeghers syndrome
Oral Nevi	Laugier-Hunziker syndrome
	Physiologic pigmentation

Melanocytomas (nevus of Ota), benevolent hamartomas common in the optic circle and the uveal tract in the pigmented races, are profoundly pigmented and, on uncommon event, have experienced dangerous change. These injuries have been depicted in cutaneous ranges (scalp) and the meninges, and, when in the spinal tract, are said to have a more forceful course. Mucosal injuries have been portrayed in the veterinary writing. Pigmented epithelioid melanocytoma is a melanocytic neoplasm with a Carney complex (myxomas, mucocutaneous hyperpigmentation, endocrinopathy) affiliation.

The sore is every now and again profoundly pigmented and happens on skin and mucosal surfaces. While it can metastasize to lymph hubs, the long haul anticipation is great [13]. Melanotic macules are basic on the lip, however they are likewise found in the oral pit. They can be broad in Peutz-Jeghers disorder and are perioral or intraoral. In Addisonian pigmentation and pigmentation caused by specific meds, the etiology includes the movement of melanocyte-animating hormone (MSH). Bronzing related with adrenal inadequacy is diffuse and ordinarily uniform. At the point when the adrenal cortex does not react to pituitary-discharged corticotropin, they proceeded with discharge exhausts corticotropin. An antecedent protein to corticotropin and MSH is discharged (professional opiomelanocortin); this protein causes the expanded pigmentation.

Medication-induced pigmentation might be tan, light and dark brown or blue-black and appear more confined and blotchy. Estrogen, chemotherapy agents (eg, imatinib, Cis-platinum, doxorubicin [14]), laxatives, zidovudine or azidothymidine (AZT), antimalarials (eg, hydroxychloroquine [Plaquenil]), and minocycline are recurrent culprits. The drugs may stimulate melanin production, may produce postinflammatory hypermelanosis, or might have metabolites that deposit in and pigment the tissues.

Medical treatment of malignant melanoma

Forceful surgery remains the treatment of decision. Medicinal treatment isn't regularly valuable for treating oral melanoma. Chemotherapeutic medicines for the treatment of oral melanoma don't dependably lessen tumor volume. Interferon, dacarbazine, and Bacillus Calmette-Guerin (BCG) antibody have been attempted with minor and erratic outcomes. Conventions with interferon (IFN) (Intron A) and different immunotherapies are normal. Multimodal treatment offers the best probability of backslide free survival contrasted and any single treatment. Kirkwood et al [15] demonstrated that surgery took after by high-measurements IFN-alfa-2b in high-chance; cutaneous melanoma gives off an impression of being more useful than surgery took after by melanoma antigen immunization. Despite the fact that not assessed in mucosal locales, these methodologies may give profitable extras to the treatment of oral mucosal melanoma. Note that INF-A use is related with discomfort, flulike side effects, fever, and myalgia.

Drug therapy (dacarbazine), therapeutic radiation, and immunotherapy are used in the management of cutaneous melanoma, but they are of questionable advantage to patients with oral melanoma. Dacarbazine is not operative in the treatment of oral melanoma; nonetheless, dacarbazine management in conjunction with interleukin 2 (IL-2) can have therapeutic value. Ipilimumab, a human monoclonal antibody, has presented positive outcomes in therapy for metastatic melanoma [16].

The drug blocks regulation of cytotoxic T-lymphocytes and permits continual immunologic activity against melanoma and other malignancies. Metastatic melanomas with either amplification of C-KIT-a transmembrane tyrosine kinase or BRAF oncogene mutation have shown tumor volume decrease with directed immunotherapy. Vemurafenib and dabrafenib have been operative in treating melanoma with a BRAF mutation [17]. Imatinib and other inhibitors of C-KIT have resulted in either partial or complete responses in patients harboring C-KIT mutations [18]. Present studies are assessing many other tyrosine kinase inhibitors in the class of imatinib [19].

Experience with oral malignant melanoma is largely derived from single cases. Anecdotal reports describe success with IFN-alfa or hyperfractionated radiation therapy. Many cancer centers follow surgical excision with a course of IL-2 as adjunctive therapy to prevent or limit recurrence. Peginterferon alfa-2b (Sylatron) has been approved by the US Food and Drug Administration (FDA) for melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. Because of the rarity of the lesions, assembling a cohort study group to assess the different therapeutic regimens is challenging. The hope is that future research will incorporate standardized multimodal therapy, for example, those used in the treatment of cutaneous melanoma.

Surgical treatment of malignant melanoma

As primary therapy, ablative surgery with tumor-free margins residues the treatment of choice if not lymph node or distant metastasis exists. Prompt surgical intervention when local reappearance is detected augments survival, as the dismal results are allied with distant metastasis. About 80% of patients with oral melanoma have local illness, and 5-10% of patients present with totally involved cervical and/or supraclavicular lymph nodes. After complete surgical excision, the local-regional relapse rate is stated to be 10-20%, and 5-year survival rates are clustered around 10-25%, with a stated range of 4.5-48%. McKinnon et al reported that tertiary care centers have the best outcomes [20].

Electrodesiccation and cryosurgery are mentioned as treatment modalities for early, superficial, palatal lesions. Conversely, partial removal outcomes in reappearance that might envelop the previous biopsy, excision, or treatment site and interfere with histologic assessment. These approaches have little or questionable advantage in the management of oral melanoma. Even though radiation alone is stated to have questionable advantage (mainly in small fractionated doses), this therapy is a valuable adjuvant in achieving relapse-free survival when high-fractionated doses are used [21]. Radioimmunotherapy trials are currently under way at many large medical centers. Surgical lymph node harvesting depends on the identification of positive nodes at clinical or imaging examination. Neither lymphoscintigraphy nor intraoperative blue-dye sentinel-node biopsy (eg, selective neck dissection) is useful in expecting drainage patterns in oral melanomas. Anatomic uncertainty seems to preclude consistent evaluation of oral lymphatic drainage patterns when this method is endeavoured. Prophylactic neck dissection (ie, elective neck dissection) is not in favour as a treatment for oral melanoma. Finally, multimodal therapy might be proven effective in the management of oral mucosal melanoma.

Prevention of malignant melanoma

Though preventive approaches for cutaneous melanoma are well known, no such approaches for oral malignant melanoma are known. Encourage patients to implement a thorough oral self-examination and to report any abnormal findings to their dentist or physician. Oral lesions that are pigmented, bleed, and mass ought to be assessed early [22]. Instruct the patient how to play out a powerful oral examination. All oral mucosal surfaces accessible for investigation ought to be pictured. This examination requires a touch of expertise and makes a beeline for reflect light properly. Satisfactory oral examination requires great lighting, a mouth reflects, and a 2 X 2-inch cloth wipes (and a lavatory reflects for self-investigation). The tongue is withdrawn and moved from side to favor the 2 X 2-inch dressing to accomplish an unhampered view. The hugest discoveries with self-examination are pigmentary changes; be that as it may, masses, ulcers, plaques, and modified sensation are additionally suggestive of threatening melanoma. Social insurance specialists can strengthen this training at follow-up arrangements and request that patients show their expertise.

Diagnosis and subsequent surgical excision of oral melanoma requires lifelong follow-up. Periodic follow-up for oral examination and assessment is necessary to evaluate for recurrence. Healthcare practitioners, including physicians, nurses, and dental personnel must encourage the patient to adopt healthy behaviors. For the life of the patient, healthcare providers must regularly perform thorough oral examinations and imaging studies to rule out recurrence and to recognize and treat oral disease. Recurrence has been described as long as 11 years after the initial surgery. Early discussions of potential problems with function, prostheses, oral fungal infection, and lesion recurrence may ensure patient compliance. At follow-up visits, dental care, nutritional status, and difficulties with the prosthesis (if necessary) can be addressed. In addition, patient comfort and function can be assessed, and the treatment or the follow-up schedule can be modified.

CONCLUSION

The improvement of new medications in the treatment of melanoma has never been as intense as at present. Single-agent chemotherapy is considered to have rather palliative effect on patients with melanoma; it is regularly well tolerated but is related with lower response rate. Detailed knowledge of protein structure and the understanding of their role in key signalling pathways in melanoma development lead to the designation of new targets for treatment of melanoma. Though the concept of a combination of immunotherapeutic and targeted agents appears to be crucial in the treatment of melanoma, the synergy between these two approaches in melanoma treatment remains controversial due to the potential increased toxicity. In the future, it is necessary to conduct further clinical trials and collect more data about overall survival, response

rates, appropriate timing and sequence of combination therapy to manage the complexity of melanoma treatment.

REFERENCES

1. **Dzwierzynski WW (2013):** Managing malignant melanoma. **Plast Reconstr Surg** ., 132: 446–460.
2. **Levine SM and shapiro RL 2012):** Surgical treatment of malignant melanoma: practical guidelines. **Dermatol Clin**., 30: 487–501.
3. **AMERICAN CANCER SOCIETY(2015):.** Melanoma skin cancer. Atlanta, Ga: American Cancer Society, Accessed at http: //www.cancer.org/acs/groups/cid/documents/ webcontent/003120-pdf.
4. **Pimiento JM, larkin EM(2013):** Melanoma genotypes and phenotypes get personal. Lab Invest.,93: 858–867.
5. **Patrick RJ, Fenske NA, Messina JL(2007):** Primary mucosal melanoma. J Am Acad Dermatol.,56 (5):828-34.
6. **Hicks MJ, Flaitz CM(2000):** Oral mucosal melanoma: epidemiology and pathobiology. Oral Oncol.,36(2):152-69.
7. **Tanaka N, Amagasa T, Iwaki H, Shioda S, Takeda M, Ohashi K *et al.*(1994):** Oral malignant melanoma in Japan. Oral Surg Oral Med Oral Pathol. ,78(1):81-90.
8. **Cress RD, Holly EA(1997):** Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians, and blacks: an analysis of california cancer registry data, 1988-93. Cancer Causes Control.,8 (2):246-52.
9. **Smith MH, Bhattacharyya I, Cohen DM, Islam NM, Fitzpatrick SG, Montague L J *et al.*(2016):** Melanoma of the Oral Cavity: an Analysis of 46 New Cases with Emphasis on Clinical and Histopathologic Characteristics. Head Neck Pathol.,(3):298-305.
10. **Rawal YB, Dodson TB, Bal HS(2017):** Oral melanoma: Relevance to the dental team members. J Am Dent Assoc.,148 (2):113-119.
11. **Prasad ML, Patel SG, Huvos AG, Shah JP, Busam K J(2004):**Primary mucosal melanoma of the head and neck: a proposal for microstaging localized, Stage I (lymph node-negative) tumors. Cancer, 100(8):1657-64.
12. **Patel SG, Prasad ML, Escrig M, Singh B, Shaha AR, Kraus DH *et al.*(2002):** Primary mucosal malignant melanoma of the head and neck. Head Neck, 24(3):247-57.
13. **Mandal RV, Murali R, Lundquist KF, Ragsdale BD, Heenan P, McCarthy SW *et al.* (2009):**Pigmented epithelioid melanocytoma: favorable outcome after 5-year follow-up. Am J Surg Pathol.,33 (12):1778-82.
14. **Li CC, Malik SM, Blaeser BF, Dehni WJ, Kabani SP, Boyle N *et al.*(2012):** Mucosal pigmentation caused by imatinib: report of three cases. Head Neck Pathol.,6 (2):290-5.
15. **Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS *et al.* (2001):**High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol., 19(9):2370-80
16. **Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA *et al.*(2010):** Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med.,363 (8):711-23.
17. **Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P *et al.*(2011):** Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med., 364 (26):2507-16.
18. **Hodi FS, Friedlander P, Corless CL, Heinrich MC, Mac Rae S, Kruse A *et al.*(2008):** Major response to imatinib mesylate in KIT-mutated melanoma. J Clin Oncol.,26 (12):2046-51.
19. **López F, Rodrigo JP, Cardesa A, Triantafyllou A, Devaney KO, Mendenhall WM *et al.*(2016):** Update on primary head and neck mucosal melanoma. Head Neck, 38 (1):147-55.
20. **McKinnon JG, Kokal WA, Neifeld JP, Kay S(1989):** Natural history and treatment of mucosal melanoma. J Surg Oncol.,41(4):222-5.
21. **Trotti A, Peters L (1993):** Role of radiotherapy in the primary management of mucosal melanoma of the head and neck. Semin Surg Oncol.,9(3):246-50.
22. **Improta G, Leone I, Donia M, Gieri S, Peloti G, Fraggetta F (2015):**New development in the management of advanced melanoma – role of pembrolizumab. OncoTargets and Therapy,8: 2535–2543.