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REVIEW

Primary mucosal malignant melanoma of the oral cavity

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Abstract Mucosal malignant melanoma arising from the head and neck region is a rare entity, and it is more aggressive than cutaneous melanoma. Furthermore, the complex anatomy of the oral cavity makes complete surgical excision difficult. Thus, early diagnosis and treatment of a mucosal lesion are important. In this study, three mucosal malignant melanoma cases and the literature have been reviewed. Three cases who presented with a primary malignant melanoma of the oral cavity have been retrospectively analyzed. All three patients were female with a mean age of 31.3 years, and the median follow-up period was 18.6 (6–36) months. The tumor was located on the maxillary gingiva in case 1 and in the hard palate–maxillary gingiva in cases 2 and 3. Case 2 had a distant metastasis during first admission. The tumor was excised with a 2-cm surgical margin in all cases. Case 2 received adjuvant chemotherapy. During the follow-up period, case 1 had a cervical lymphadenopathy 8 months after the first operation, so she underwent cervical lymph node dissection then received chemotherapy. Melanoma of the oral cavity is very rare with an extremely poor prognosis. As some melanomas may be amelanotic, a high index of suspicion is necessary. A biopsy should be taken from any suspicious lesion in the oral cavity. Surgical excision combined with adjuvant therapy is the main treatment approach for these cases. Prognosis of the disease depends on early diagnosis and treatment. A multicenter prospective study is required to introduce staging of the disease and the optimal treatment regimen.

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Introduction

Melanocytes are derivations of neural crest tissue and are widely distributed throughout cutaneous and mucosal surfaces. The function of melanocytes in mucosa is not clear. In physiological states, the melanocytes in mucous membranes do not produce melanin and contain only nonmelanized melanosomes in their cytoplasm.

Primary mucosal melanoma of the head and neck is a rare disease, accounting for approximately 0.2–8.0% of all melanomas [5, 18, 21, 30]. Of all mucosal melanomas, 55.4% are found in the head and neck [3, 31, 34]. Most of these lesions (80%) have occurred on the maxillary anterior gingival area, especially on the palatal and alveolar mucosa [2, 4, 14, 17, 27, 30]. Other reported locations of the lesion include the lower and upper labial mucosa, buccal mucosa, and tongue. Mucosal melanoma can rarely be found in the pharynx, larynx, or upper esophagus.

Sunlight is not an important etiologic factor for the mucosal melanoma, unlike its cutaneous counterpart. Although some factors have been implicated in the development of this malignancy, such as solar irradiation, mechanical trauma, ill-fitting dentures, oral hygiene, self-medication, and exposure to formaldehyde and carcinogenic compounds in the air, the potential role of these compounds is unclear.

The incidence of malignant melanoma arising from the mucosal surfaces is higher in India, Africa, and Japan than in western countries. There is a relatively higher incidence of melanoma of the oral cavity in Asian people [3].

Although they generally occur as asymptomatic masses, mucosal melanomas show far more aggressive behavior as compared to skin melanomas and are more inclined to metastasize into regional and distant sites with a rate of 5–48% of regional and 4–14% of distant dissemination, resulting in a high rate of cause-specific death, with 5-year survival rates reportedly ranging from 0% to 55% [13, 20]. In this study, we presented three cases with mucosal malignant melanoma in the oral cavity, and the literature was reviewed.

Patients and methods

Case reports

Case 1

A 36-year-old female patient presented with an asymptomatic, progressively enlarging firm mass on the maxillary inter-incisive gingival area for 3 months. Initially, she went to a dentist, who took a biopsy from the lesion, and then, she was referred to our clinic with the pathology result confirmed "mucosal malignant melanoma." She was a non-smoker and did not consume alcohol.

On clinical examination, a pigmented, firm, solid tumor 1×1.5 cm in size in the inter-incisive gingival region with hyper-pigmented areas was found. There were no lymph nodes on the neck. CT of the maxilla showed that there was no erosion in the maxillary alveoli. There was no sign or symptom of distant metastasis on the investigation. The tumor was excised with a 2-cm surgical margin, and the defect was closed with an upper buccal flap (Figs. 1 and 2). The pathology report of the surgical specimen revealed that there was no tumor on the surgical margins and it was an early-stage tumor (level 2).

A lymphadenopathy 8 months after the first operation was found on the level 2 of the neck during the routine follow-up.

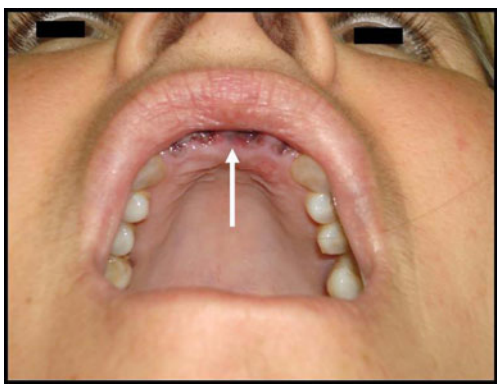

Fig. 1 The tumor on the inter-incisive gingival region with hyper-pigmented areas (preoperative)

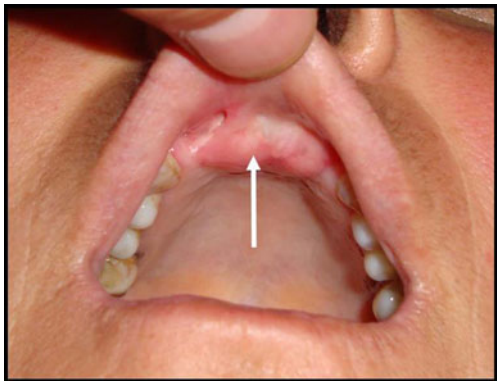

Fig. 2 The tumor excised and the wound healed up with upper buccal flap (postoperative)

A right modified elective radical neck dissection was performed, and the pathology report confirmed that one out of 23 lymph nodes was involved by the tumor. She was also referred to the oncology department and had chemotherapy. There was no clinical evidence of local or distant metastases of the tumor in the 2-year follow-up period.

Case 2

A 26-year-old female patient presented with an ulcerated pigmented lesion invading the hard palate, soft palate, and the alveolar and vestibular mucosa of the maxillary gingiva, 3×7 cm in size, and a 3×2-cm-sized lymph node was present on the submandibular region. The history of the patient revealed that she had had asymptomatic pigmented macules and patches on the palatal mucosa for many years until 1 year ago, when she noticed an enlarging mass on the palate. There was a destruction of the hard palate underneath the lesion on the maxillary CT. A small incisional biopsy from the mass was performed, and the pathology report confirmed that it was a "malignant melanoma." MRI for the distant metastasis investigation detected a 1×1.3-cm mass in the temporal lobe of the brain. Whole-body positron emission tomography was performed, and a hilar lymph node in the right hemithorax was also detected. The staging of the tumor was accepted as a level 3 N1 M1.

Partial maxillectomy for palliative treatment and soft tissue reconstruction were performed through buccal mucosal flap (Figs. 3, 4, 5). No surgical intervention was considered for the brain and the lung metastasis. The patient was referred to the oncology department for adjuvant therapy post-operatively, and she died 8 months later.

Case 3

A 32-year-old female patient presented with a history of a 3×2-cm ulcerated lesion on the left palatal mucosa for

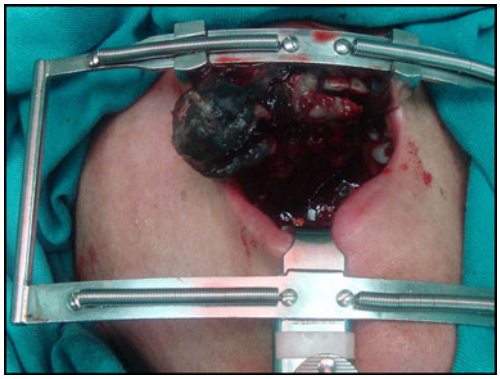

Fig. 3 An ulcerated pigmented lesion invaded the hard palate, soft palate, and the alveolar and vestibular mucosa of the maxillary gingiva (preoperative)

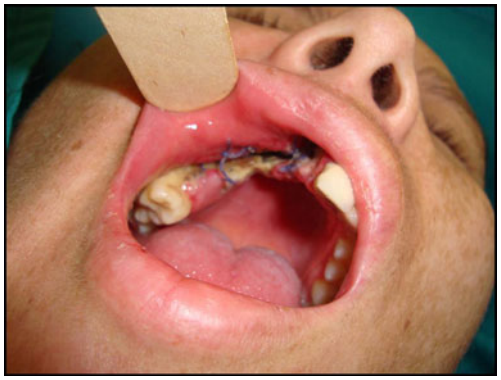

Fig. 5 The tumor excised and defect closed with a buccal mucosal flap (postoperative)

3 months. There was no palpable node on the neck. Computerized tomography of the lesion and the chest did not reveal any bone erosion and distant metastasis. A small incision biopsy was performed, and the pathology report confirmed that it was a malignant melanoma (Figs. 6 and 7). The lesion was excised with a 2-cm surgical margin, and the defect was closed with a radial forearm free flap. The pathological report revealed that the malignant melanoma was completely excised, and the level of the tumor was 2. There is no clinical evidence of distant metastases or local recurrence of the tumor during the 3-year follow-up period.

Discussion

Oral mucosal melanomas mostly occur on the palate and gingiva, with the maxillary arch being affected in 80% of cases [2, 4, 14, 17, 18, 30]. They may also be seen in the buccal mucosa, mandibular gingiva, lips, tongue, and the base of oral cavity, in decreasing frequency [12, 19, 24]. The clinical appearance of oral melanomas may be black, gray, purple, red, or even white in color. Grossly noticeable pigmentation occurs in approximately 75% of cases. Melanin pigment is noted in almost 90% of lesions [28]. The delay in diagnosis is most likely due to the fact that lesions on mucosal surfaces are inaccessible and not easily seen, and there is usually no pain at the beginning; patients do not seek treatment until the tumor reaches an advanced stage; then, they eventually have swelling, bleeding, pain, or loosening of teeth [24, 27].

A mucosal melanoma of the head and neck region has a peak incidence in patients aged 60–80 years. The median age of patients is typically 20 years later than that for cutaneous melanoma [3, 15].

Many investigators report a male to female ratio of 2:1 [3]. Others claim that there is only a slight predilection for male predominance or no sexual predilection at all [30, 33]. However, our three patients were female, and the mean age was 31.3 years.

In contrast to cutaneous melanomas, mucosal melanomas present a more aggressive vertical growth phase with invasion of the underlying submucosa. The lack of a radial growth phase is, in turn, associated with a poor prognosis

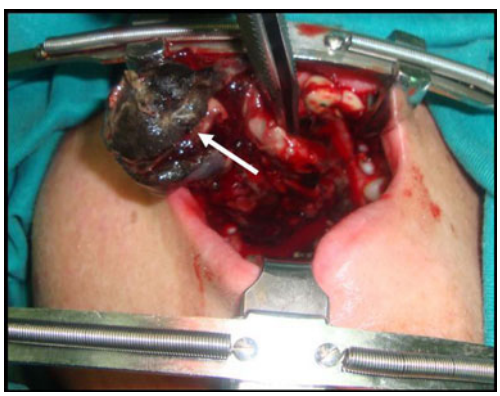

Fig. 4 Excision of the tumor (intraoperative)

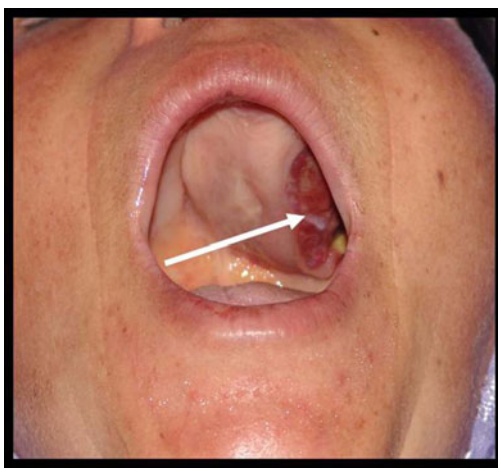

Fig. 6 A 3×2-cm ulcerated lesion on the left palatal mucosa

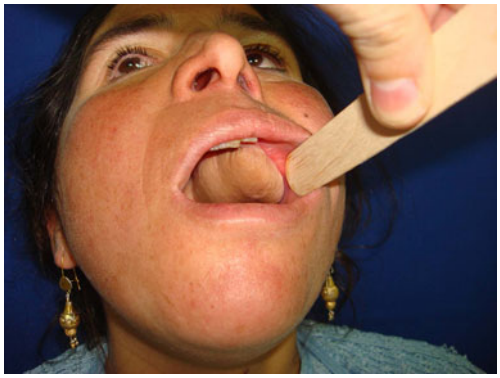

Fig. 7 The tumor excised and the defect closed with a radial forearm free flap (postoperative)

compared to cutaneous melanomas. The traditional histological staging for cutaneous melanoma (such as Breslow, Clark level) cannot be applied to the mucosa because the mucosa lacks histological landmarks analogous to the papillary and reticular dermis. Breslow thickness, the single most important histological prognostic factor in localized cutaneous melanoma, has not proved to be useful in head and neck mucosal melanomas [23, 32]. Therefore, the Memorial Sloan Kettering Cancer Center classified the tumors into three groups according to the depth of invasion:

Level I: In situ mucosal melanoma without invasion or with microinvasion predominantly above the epithelial basement membrane

Level II: Invasion up to the lamina propria, below the epithelial basement membrane but above the perimysium, periosteum, or perichondrium

Level III: Deep invasion of the perimysium, periosteum, or perichondrium [22, 23]

The levels represent different microanatomic compartments separated by tissue barriers that are easily and reliably identifiable on light microscopy [1, 6, 7].

Prognostic factors of the mucosal melanomas also depend on anatomic site, the size (largest dimension), thickness, level of invasion, ulceration, mitotic index, necrosis, vascular invasion, and nerve/nerve sheath involvement by the tumor. Radiologic evidence of the bony erosion has been associated with early hematogenous spread [24]. In case 2 with x-ray evidence of bony erosion, the survivability was 8 months.

Goerres et al. [9] showed that positron emission tomography and 18F-fluorodeoxyglucose may be suitable for the staging and/or restaging of these patients.

Because of its rarity, mucosal melanoma is poorly understood, characterized, and studied. Therefore, there are yet no clear staging of the disease and consensual approach to treatment. Many studies report that a wide surgical excision with clear margins as the primary treatment offers the best chance of obtaining local control and greater survival rates [11, 16, 26]. Systemic chemotherapy is used in patients with advanced stage in which response to therapy is associated with prolonged survival rates. Our case 2 had adjuvant chemotherapy, and case 1 received chemotherapy after having a submandibular lymph node involved by the tumor. The main goal of therapy for the patients with metastatic malignant melanoma is palliation. Many patients have been treated with postoperative radiotherapy even though the melanoma is believed to be radioresistant. Irradiation therapy may be preferred occasionally as a primary modality in the elderly, medically compromised patients and when distant metastasis is evident [26]. If surgery cannot be performed with wide margins, especially for patients with mucosal tumors, postoperative radiotherapy may be beneficial [26]. Complete or partial response has been reported with exclusive radiotherapy, and postoperative radiotherapy appears to increase the rate of local control, independent of the primary tumor stage. Our case 2 received radiotherapy for the palliation of the brain metastasis.

The lack of a standardized therapy received by the patients remains a weakness of the current study. As a consequence of surrounding vital structures, positive surgical margins following excision are not rare. Therapeutic neck dissection is indicated for lymph node metastasis in the neck. The issue of sentinel node biopsy, which has achieved great acceptance in the treatment of cutaneous malignant melanomas, has not been studied in mucosal melanoma.

Delay in the diagnosis, the complex anatomy of the oral cavity which makes complete surgical excision difficult, the rich vascular supply leading to early hematogenous spread, and the more aggressive nature of oral tumors may all result in a poor prognosis [10, 24]. Overall, 18% of patients have lymphatic metastasis at presentation. The average rate of distant metastasis at presentation is 10%. Mucosal melanoma tends to metastasize to the lungs, liver, brain, and bones [21, 25, 30]. The 5-year survival rate in mucosal melanoma is 8% to 30% [8, 21, 24, 25, 29, 32, 33].

Conclusions

Primary melanoma arising in the mucous membranes is an unusual clinical entity. Currently, despite aggressive therapy, the prognosis of patients with mucosal melanoma is extremely poor. Surgery remains the mainstay of treatment, but it offers long-term cure only to a limited number of patients; hence, adjuvant therapy which leads to a temporary shrinkage of the tumor should be considered. A multicenter prospective study is required to introduce staging of the disease and optimal treatment regimen.

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