Report of a recurrent tongue malignant melanoma and review of literature

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Abstract

Primary oral mucosal melanoma is a rare disease. Etiopathogenesis of oral mucosal melanoma (OMM) is inadequately understood. The prognosis of OMM is very poor . Due to its low incidence and late recognition, the optimal treatment modality is not well established. Surgery with free margins is the mainstay of treatment.

Introduction

Primary oral mucosal melanoma (OMM) is a very uncommon entity that makes up about 1-8% of all malignant melanoma and less than 0.5% of all oral malignant tumors.[1,2]OMM arises from oral melanocyte which seems to be part of the oral immune system.[1,3]

Maxillary gingiva and hard palate are the most common sites of primary OMM. The tongue specifically is an infrequent site and represents less than 2% of all oro-nasal melanoma cases. [4] To the best of our knowledge regarding English literature review, about 30 cases of primary malignant melanoma of the tongue were reported.

OMM has different etiohistopathology, genetic mutation, and prognosis compared to cutaneous malignant melanoma. The exact etiology of OMM is still unknown. Although alcohol consumption, tobacco use, cigarette smoking, and denture trauma are reported to affect the occurrence of OMM.[5,6] Most of them are thought to be De Novo. Oral pigmentation precedes the development of malignant melanoma in about one-third of the patients.[4,7] However, the mechanism of this transformation is not clearly understood yet.[8,9]

Oral melanoma can manifest as a macule, plaque, or mass. Therefore, they are very easy to diagnose clinically because of their appearance in contrary to nasal mucosal melanoma which cannot detect or diagnose easily due to their location. However, they are often asymptomatic and connived or misdiagnosed as benign pigmented lesions until advanced stages when they become ulcerative or hemorrhagic, or painful. Delayed diagnosis can be one of the reasons for the poor prognosis of OMM.[9]

Early detection and treatment would improve the prognosis significantly.[10] The treatment modality of choice is not well depicted due to its rarity and poor prognosis. Radical surgery currently is the "gold standard" and main treatment of OMM. It can be combined with neck dissection, depending on cervical lymph node status. Non-surgical treatment options, like radiotherapy and medical therapy (e.g., checkpoint inhibitors), can be used as adjuvant treatment depending on stage.[1] The size and depth of the tumor, lymphovascular invasion(LVI), necrosis, polymorphic neoplastic cells, lymph node involvement, and metastasis straightly affect the prognosis.[11] The five-year survival rate of OMM is about 15–38% which is the lowest among other melanoma.[3]

Melanomas of the oral cavity and tongue are commonly found in patients older than 40 years, and males are affected slightly more than females.[10]

The early asymptomatic phase and difficulty in gaining complete radical excision with safe margins are two important factors that contribute to a bad prognosis. Hence, consideration of malignant melanoma in the differential diagnosis of pigmented as well as non-pigmented lesions of tongue and oral mucosa is critical, regardless of the age of the individual. The thorough clinical examination followed by histopathological and immunohistochemical study in suspicious lesions is imperative to rule out oral melanoma.

We present a rare report of a young woman with a recurrence of tongue melanoma while on maintenance treatment with imatinib^{R}, who was treated by partial glossectomy with submental flap reconstruction and adjuvant radiotherapy.

Case report

A 33 years old woman presented to our clinic with a pigmented mass with ulceration in the left posterolateral part of her tongue that was gradually growing five months before her presentation. There was a 1 cm pigmented ulcerated mass with a satellite smaller discoloration adjacent to it without palpable cervical lymphadenopathy on physical exam. An incisional biopsy was taken that turned out to be malignant melanoma. MRI showed an enhancing lesion measuring about 14 mm ×6 mm at the posterolateral part of the tongue without cervical lymphadenopathy. There was no evidence of distant metastasis in chest abdominopelvic CT scan. The patient has no history of smoking or alcohol use. Medical history was noncontributory. Partial glossectomy with safe margins was performed, and the defect was reconstructed with a local flap. Pathology revealed malignant melanoma with satellite lesions with a maximum thickness of 5-6 mm. Striated muscles were infiltrated by tumors. Lymphovascular invasion was present. There was evidence of macroscopic and microscopic satellite nodules. All surgical margins were free. She refused postoperative radiotherapy but was under maintenance imatinib^{R} treatment due to the strong positivity of C-KIT.

On her regular follow up there was no evidence of recurrence for about two years. Then after, she noticed a black spot on her tongue that gradually increased in size without any accompanying symptoms. Physical examination revealed a 15 mm×10 mm pigmented mass at the left posterolateral portion of her tongue, it was indurated and non-tender without ulceration. There were no other similar lesions intraorally or elsewhere on her body. MRI of the neck revealed an enhancing lesion measuring about 14.6 mm at the left posterolateral portion of the tongue related to the patient's known pathology. Incisional biopsy of the lesion revealed malignant mucosal melanoma. PET scan and neck ultrasonography revealed no evidence of distant metastasis or local lymphadenopathy. Her condition was discussed at the multidisciplinary tumor board, and she became a candidate for surgery and adjuvant radiotherapy. Therefore, she underwent a partial glossectomy. Fig1. The frozen section confirmed tumor margins were free of malignant cells and the defect reconstructed with a submental flap. Her post-op course was uneventful. The pathology report revealed T3N0 malignant melanoma with safe margins. Fig2. Maximum tumor thickness was 8 mm, ulceration was present, microsatellite lesion was not identified, there was no evidence of lymphovascular invasion nor neurotropism. Mitotic rate was 4 mitoses per mm^2. Adjuvant Radiotherapy started about one month after surgery. She is currently undergoing regular follow-up. No local recurrence of the lesion was found during the 3-month follow-up period.

Discussion

Malignant melanoma is an aggressive tumor that originates from melanocytes derived from neural crest cells in the basal layer of the epithelium. Malignant melanoma of the oral cavity mucosa is a distinctly rare entity with an incidence of 0.2-0.8% of all malignant melanoma, it was first described by Weber in 1859. [1.4.7] The common sites for intraoral melanoma are the palate and maxillary gingiva which account for 80–90 % of the cases, but any mucosal site may be involved.[1.2] Tongue melanoma is extremely rare and makes up about 2.3% of all oro-nasal melanoma.[5.7]There are about 30 cases of tongue melanoma reported in English literature. Most cases of oral and tongue melanoma occur between the fourth and the seventh decade of life and have a predominance for the male gender with a male to female ratio of 2.8:1.6. [13.14] However there is no gender difference regarding some studies.[4.15.16] It is diagnosed approximately a decade earlier in males than

in females.[10] It affects races differently and Japanese are especially more susceptible to OMM that can point to genetic or environmental susceptibility that is not identified yet.[4.10] We presented a young woman with a history of primary tongue melanoma two years ago who presented with recurrence of tongue melanoma while being on maintenance imatinib^{R} treatment.

The etiology of OMM is unknown. According to the literature some environmental factors and habits like alcohol consumption, cigarette smoking, denture irritation, and trauma may have some effect on its occurrence. But the majority of them are believed to be De nova. [10.15]Mucosal melanosis was related to oral malignant melanoma in 66% of cases, pre-present in 36.2%, and synchronous in 29.8% of patients according to Takagi and colleagues report.[4.7.17] Many genes are involved in the occurrence of melanoma, including CDKN2A (p16), CDK4 (chromosome 12q15), RB1, CD- KN2A (p19), and PTEN/MMAC1 that can be targeted for systemic therapy.[13] Our patient has no risk factors relating to the etiology of mucosal melanoma, which is in favor of the current belief that most oral mucosal melanomas emerge De novo.

OMM can present as an asymptomatic pigmented macular or nodular lesion in the oral mucosal membrane and some cases without any pigmentation as an amelanotic lesion. The surface may be smooth and intact or ulcerated.[16.18] Satellite foci may siege the primary tumor.[2.13] By the way, as they are asymptomatic and most people don't inspect their oral cavity precisely, even pigmented variants usually are diagnosed late at an advanced stage when they become painful, hemorrhagic, and ulcerative. The clinical manifestation of OMM may differ broadly and is intersected according to Tanaka et al study into pigmented nodular type, pigmented macular type, pigmented mixed type, non-pigmented nodular type, and non-pigmented mixed type. [13.19] Signs and symptoms of OMM contain bleeding, ill-fitting dentures, pain, increment mobility of teeth, and deferment healing of extraction sockets.[2]

OMM has a dismal prognosis that is somehow related to late diagnosis and advanced stage of the disease. So, any suspected lesion in the oral cavity should be biopsied and sent for histopathologic examination. Excisional biopsy with 1-2 mm margin for small lesions and incisional biopsy from the bulkiest or more suspected part of the large lesion is obligatory .[2]OMM can be diagnosed by hematoxylin and eosin staining. However, immunohistochemically markers, such as HMB45 and Melan-A, would be used for confirming the diagnosis.[14]

The most significant histopathologic finding is the proliferation of neoplastic melanocytes with nuclear changes. They can form in different phenotypes such as epithelioid, spindle, or fusiform, which are arranged in asymmetric shape architectures. There is a conquest of cells with a plentiful eosinophilic, clear cytoplasm, and melanin granules in the dermo-epidermal junction. They depict high mitotic activity and sometimes have Necrosis and ulcerations.[3.19]

According to Greene et al in 1953, the lesions with the following criteria are regarded as primary malignant melanoma of the oral cavity: 1) histological and clinical verification of malignant melanoma; 2) the existence of junctional activity, and 3) the incapacity to denote any other primary site. [12.16] So according to this criterion, our patient was considered as primary tongue melanoma at first presentation two years before the recent complaint.

There are several staging systems for malignant mucosal melanoma based on the TNM staging system, micro invasion, histopathologic pattern, and so on that neither of them is commonly utilized. Ballantyne explained a three-level staging system for classifying mucosal melanomas in 1970, which continues to be widely used. Stage I is the presence of the primary tumor ($T_{any}N_0M_0$) without lymph node involvement or distant metastasis, that itself spitted into three levels; level I is pure in situ melanoma with either lack of invasion or with micro invasion, in level II lamina propria is involved, level III is permeation into the deep skeletal tissue. Stage II is regional lymph node involvement ($T_{any}N_1M_0$) and stage III is tumor distant metastasis (T_{any} $N_{any}M_1$).[2.13.19.20]

The American Joint Committee on Cancer (AJCC) staging system (8^{th} edition,2018) for OMM begins with stage III as the most limited form of the disease (T3, N0). Stage IV is divided into three parts, IV A consists of (T3N1) or (T4a, N0 or N1), Stage IV B (T4b, N0 or N1), and stage IV C (any T, any N with metastasis).

table.1.

T category	T criteria
T3	Limited to the mucosa and immediately underlying soft tissue irrespective of thickness or greatest dimension
T4	Moderately or highly advanced
$T4_a$	Involving deep soft tissue ,cartilage ,bone ,or overlying skin
$T4_b$	Involving brain, dura ,skull base ,lower cranial nerves (IX, X , XI, XII),masticator space ,carotid artery ,preve

Table 1. The American Joint Committee on Cancer (AJCC) staging system,T:Tumor (8^{th} edition,2018)

Prasal et al and Patal et al proposed classification for mucosal melanoma with negative cervical lymph node involvement based on micro invasion as follows: Stage I is melanoma in situ (non-invasive), Stage II is the one invading the lamina propria and Stage III is the one invading deeper tissues. [12.19.]The Clark and Breslow classifications have not been accepted as prognostic predictors in oral malignant melanoma due to architectural differences between oral mucosa and skin.[10.12] The oral mucosa is thinner than skin and lacks histological points of reference similar to the papillary and reticular dermis.[21] Most authors use the classification of the Western Society of Teachers of Oral Pathology (WESTOP), which divides them into a relatively simple system in relation to its histopathological pattern as (a) melanoma in situ, delineated to the epidermis and its junction with the connective tissue; (b) invasive melanomas, in which the neoplasia pervades into the connective tissue and (c) melanomas with a merged pattern between invasive and in situ.[12.13.22.23]

In the case of a suspected tumor, CT and MRI can be used for evaluation of the loco regional extent of the lesion that is fundamental for defining resectability of the tumor, MRI is the modality of choice for more accurate investigation.[10.19] According to current German guidelines, a clinical examination is enough for in situ melanoma staging. Head MRI, whole-body imaging like PET-CT, CT, or skeletal scintigraphy combined with LDH and tumor marker S100B are used in advanced stages .[1]

Optimal therapeutic management of OMM is still controversial. Multimodality management may be more beneficial in the treatment of mucosal melanoma.[23] Radical surgery with negative margins of the primary lesion is the cornerstone of treatment.[15.19.24.25] The safe margin of the OMM is at least 1.5 cm according to the National Comprehensive Cancer Network (NCCN) like SSC of the oral cavity, and 2.5 cm for lesions larger than 3 cm.[2.13] Although complete excision of the tumor is essential, the extent of safety margins has not been clearly clarified. [26]

If wide free margins (like 3 cm) are leading to serious morbidity, the surgeon can decrease it to just negative margin (like 5 mm) because there is no survival difference considering the size of safety margin.[22.26.27]

Neck dissection should be added in cases with preoperatively confirmed lymph node metastasis. Prophylactic lymph node dissection is not recommended due to lack of effect on survival .[12 .19.26.28.29.30]

Sentinel Lymph Node Biopsy(SLNB) that is currently used in cutaneous melanoma, and early-stage head and neck squamous cell cancer (T1, T2), is not usually performed at OMM however it is technically possible.[31.32.33] SLNB can be used to investigate the neck of patients with OMM and may create another option to define patients who would-be candidates for elective neck dissection.[.30.34.35.36]The presence of a microscopic metastatic focus in the sentinel lymph node was associated with early hematogenous dissemination according to Starek et al study.[23..37] SLNB is not standard of care and can be used as a prognostic factor and a potentially efficient staging tool in mucosal melanoma, albeit few studies applied SLNB in OMM and further investigation is warranted.[12.30.38.39.40]

Radiotherapy, chemotherapy, immunotherapy can be added to surgery, although their effectiveness is unknown.[2.23] Poor prognostic pathologic features like multiple positive nodes, or extra nodal extension of metastatic melanoma are indicators for post-operative radiotherapy;[2.19.25] however, OMM is considered as radio resistance, it can help to achieve local control despite not improving overall survival. [12.41] A tumor

thickness greater than 5 mm, presence of vascular invasion, necrosis, polymorphous tumor cell morphology, positive margins, primary site, bony invasion, and systemic metastasis have been associated with poor survival in patients with primary OMM.[2.11]

The lesions that are discovered early and eliminated before the occurrence of metastases will have a better prognosis and are correlated with higher survival rates.[4] Independent predictors of recurrence were the head or neck site of the primary tumor, ulceration, thickness, and mitotic rate greater than $3/mm^2$, SLNB positivity, and signs of rapid tumor growth.[31]

After the individual mutation status has been determined, targeted systemic therapy using BRAF, MEK, KIT, or checkpoint inhibitors can be carried out to extend overall survival with an acceptable rate of side effects.[1.19] C-KIT is a key regulator of growth, differentiation, migration, and proliferation of melanocytes. Activating mutations in the c-*KIT* gene are detected in a significant number of about 80% of patients with mucosal melanoma. [21]The mitogen-activated protein kinase (MAPK) pathway (RAS/MEK/ERK) is a critical growth cascade in oral mucosal melanoma.[12] Immunotherapy is useful in the treatment of malignant melanoma at high risk for recurrence and metastatic melanoma.[23.34]

In patients with recurrent diseases and without distant metastasis like our patient, the second surgical resection seems to be the best option if the lesion can be completely resected without considerable morbidity. Surgical procedures can salvage up to 25% of patients with local recurrence.[34]

Oral melanomas are more aggressive and have a higher tendency for metastasis than other oral cancers or cutaneous melanomas.[8.12] The more aggressive behavior of OMM has been related to angioinvasion, anatomic relation that prevents sufficient surgical removal, and delay in diagnosis, the tendency to early ulceration due to repeated trauma, which in turn can cause pathways for metastasis and a higher rate of regional and systemic spread. [13.26] About 25% of patients with OMM present with lymph node metastasis.[2.10.12.34]

Late diagnosis often coincides with an extensive metastatic tumor.[7] After surgical ablation, recurrence and metastasis are frequent events, and most patients die of the disease in 2 years. A review of the literature indicates that the 5-year survival rate is within a broad range of 4.5%–48.0%, but most are within the range of 10.0%–25.0%.[4]

The absence of early signs and symptoms, the lack of evidence-based treatment, the early development of metastases, and high rates of local recurrence contribute to the overall poor prognosis of these melanomas.[15]

In this article, we report a case of primary malignant melanoma of the tongue that underwent adequate surgery and adjuvant immunotherapy. During her close follow-up care, an early recurrence was detected, and she underwent standard surgery with adjuvant radiation therapy.

Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' contribution: All authors were involved in data collection, interpretation, drafting the article, revision of the manuscript, and the final approval of the version to be published.

Ethics statement:

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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