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Case Report

Treatment of Primary and Metastatic Multifocal Mucosal Melanoma of the Oral Cavity with Imatinib

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Abstract
Background: Mucosal melanoma of the oral cavity is a rare entity and accounts for less than 1–3% of all melanomas. Contrary to cutaneous melanoma, primary oral melanoma more commonly harbors mutations in c-KIT. ***Methods:*** A 64-year-old man presented with asymptomatic, multiple, brown-to-black macules in the oral cavity. A biopsy was taken and histopathology exhibited mucosal melanoma. In molecular analysis, a c-KIT mutation was proven and a CT scan revealed pulmonary metastases. Due to the multifocality of the lesions, the metastases, and the mutation status, a therapy with imatinib was initiated. ***Results:*** After 1 year of therapy, progressive disease in the lung was noticed. Therefore, the therapy was switched to a PD-1 antagonist and a CTL-4 antibody. ***Conclusions:*** Our case suggests that imatinib may be considered as first-line treatment for both locally advanced and distant primary multifocal oral melanoma, for which surgery or radiotherapy of the primary tumor is impossible.

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Case Presentation

A 64-year-old man was referred to our outpatient clinic because his dentist noticed multiple black-to-brown patches in the oral cavity. The patient had noticed the onset of pigmentation about 1 month before. His past medical history was unremarkable, and he denied having symptoms such as burning and itching or using tobacco. A clinical examination revealed multiple, partially confluent, brown-to-black macules in the whole oral cavity involving also the base of the tongue and the hard palate (Fig. 1). A differential diagnosis of melanosis versus mucosal melanoma was made and a punch biopsy was taken. Histopathology exhibited mucosal melanoma (0.4 mm thickness; 2 mitoses/mm^2). A molecular analysis of the specimens showed a c-KIT V560D mutation. BRAF and NRAS mutation assessments were negative. Laboratory test results including lactate dehydrogenase and S-100 levels were within normal ranges. Radiographic staging including whole-body CT scanning showed pulmonary metastases.

The case was presented to the interdisciplinary tumor board, where neither surgery nor radiotherapy was considered as a possible option to treat the primary tumor. Because of the locally advanced primary tumor and the metastases, and based on the mutation status, a targeted therapy with the tyrosine kinase inhibitor imatinib (400 mg once daily) was recommended and initiated. Three months later, a whole-body CT scan was performed, on which stable disease was noted. Moreover, the lesions in the oral cavity showed signs of regression, so that it was decided to continue the therapy. Regular follow-up and imaging evaluations every 3 months revealed stable disease of the pulmonary metastases and a partial response of the primary melanoma (Fig. 2). However, at the last follow-up 14 months after treatment initiation, the CT scans revealed progressive disease in the lung. For this reason, the treatment with imatinib was stopped. The patient currently receives combination therapy with a PD-1 antagonist (nivolumab) and a CTL-4 antibody (ipilimumab).

Discussion

Our case highlights several problems related to the early diagnosis and adequate treatment of multifocal primary oral melanoma. First, mucosal melanoma of the oral cavity is considered an exceedingly rare but highly aggressive form of melanoma, accounting for less than 1–3% of all melanomas. Accordingly, there is poor awareness about this melanoma subtype in the general population. Moreover, there are no defined risk factors such as a high nevus count or sun exposure habits that would help identifying persons at risk of developing oral mucosal melanoma. Although mechanical trauma, chronic infections of the oral cavity, and tobacco use were discussed as possible causal factors, their exact etiological role is still unclear [1–4].

Second, oral mucosal melanomas most commonly affect the hard palate or the maxillary alveolus. Occasionally, multiple foci are seen. The hidden localization and initial lack of symptoms may hamper early detection by the patient. In fact, the data suggest that melanoma of the oral cavity is often diagnosed at an advanced tumor stage (i.e., the 5-year relative survival is 25.5% for mucosal melanomas of the head and neck) [1–4].

Third, its clinical presentation is highly variable, with a broad spectrum of differential diagnoses such as mucosal melanosis, amalgam tattoo, mucosal nevi, lingua nigra, or even other infectious or inflammatory disorders [1–4].

Forth, surgery is considered the mainstay in treating oral mucosal melanoma, followed by adjuvant radiotherapy. However, such treatment is often challenging, especially in the case of multifocal primary tumors. In our patient, surgery and radiotherapy were considered noncurative given the large extension of the primary tumor [1–4].

Fifth, in contrast to cutaneous melanoma, which shows BRAF mutation in 50% and NRAS mutation in about 20% of cases, primary oral melanoma more commonly harbors mutations in c-KIT. Although enormous progress has been made in the successful treatment of advanced cutaneous melanoma using targeted therapy and immune checkpoint inhibitors, the response rates and outcomes in the setting of metastatic mucosal melanoma are less promising. In particular, there is very limited knowledge about the use of targeted therapies in the treatment of primary mucosal melanoma [4, 5].

In the case of inoperable, locally advanced, or metastatic melanoma, systemic therapy is indicated. In this regard, an exact definition of the mutation status is unavoidable, since targeted therapies nowadays are considered first- or second-line therapies.

The recent retrospective analysis by Kim et al. [6] demonstrated BRAF inhibitors to be very effective in BRAF-mutated metastatic melanomas regardless of their subtype (cutaneous, acral, or mucosal). Altogether, 27 patients with $BRAF^{V600E}$-mutated metastatic melanoma were included; 19 of them suffered from mucosal and acral melanoma. The objective response rate (ORR) was comparable in both groups (78.9% in the mucosal/acral melanoma group and 75.0% in the cutaneous melanoma group). The median progression-free survival (PFS) of all patients figured up to 9.2 months. PFS, however, was significantly better in patients who received a combination treatment with dabrafenib and trametinib than in those who were treated with vemurafenib alone. The ORR was nearly the same in both therapy regimes.

However, BRAF mutations are rarely seen in mucosal melanomas, with a reported frequency of 3.6–16.5%. Instead, nearly 25% of mucosal melanomas show a genetic aberration in KIT, a receptor tyrosine kinase [7–9]. Currently, the KIT inhibitor imatinib has been approved for the treatment of KIT-mutated melanoma. Imatinib is a tyrosine kinase inhibitor with potency against abl, c-kit, and platelet-derived growth factor receptor-β. The safety and efficacy of doses ranging from 400 to 800 mg daily have been well established. Besides its application in metastatic, KIT-mutated melanoma, it is used in patients with chronic myeloid leukemia and gastrointestinal stromal tumors [8].

It has to be emphasized that the response rates to the therapy significantly differ depending on the KIT mutation status. In fact, Hodi et al. [7] reported data from a clinical trial using imatinib in metastatic mucosal, acral, or chronically sun-damaged melanomas. Overall, 24 patients were included; 8 patients had a KIT mutation, 11 showed KIT amplification, and 5 had both. The response rates to imatinib amounted to 54% in the mutated group and 0% in the amplified group. Furthermore, 4 patients in this study had an NRAS mutation before treatment; none of these had a response to or sustained stable disease with imatinib. These findings again confirm the model describing both the PI3K and the MAPK pathway as important downstream outputs in activated KIT in melanoma [7, 9].

In a retrospective analysis, Postow et al. [10] investigated the efficacy and safety of ipilimumab in patients with unresectable or metastatic mucosal melanoma. Twenty-two of the 33 included patients showed immune-related progressive disease 12 weeks after treatment with ipilimumab. The median overall survival was 6.4 months, and although durable responses to ipilimumab were observed, the overall response rate was much lower than in cutaneous melanoma [10]. In a series of 71 patients in the Italian “early access program,” a

response rate of 12.5% and a 36% rate of stable disease with pretreated metastatic mucosal melanoma was observed [2, 11].

A recently published retrospective trial confirmed the response rates to anti-PD-1 agents in mucosal melanoma to be comparable to the rates in patients with cutaneous melanoma [12]. The patients received either pembrolizumab or nivolumab as a monotherapy. The ORR was 23% and the PFS amounted to 3.9 months. A variety of trials using nivolumab, nivolumab plus ipilimumab, or ipilimumab alone have proved an advantage of nivolumab in the treatment of mucosal melanomas. The median PFS and response rate was 2.96 months and 23.2% for nivolumab, 5.85 months and 37.2% for nivolumab plus ipilimumab, and 2.69 months and 8.3% for ipilimumab, respectively [2, 13].

In the most recent study by D'Angelo et al. [14], the efficacy and safety of nivolumab alone or in combination with ipilimumab in mucosal and cutaneous melanoma were compared. It became apparent that, independently of the melanoma subtype, the median PFS and the ORR were much lower in the nivolumab-alone group than in the combination therapy group. Furthermore, grade 3 or 4 treatment-related adverse events were more frequent with the combination therapy, but comparable for both mucosal and cutaneous melanomas [14].

Conclusion

In case of localized disease, surgical resection is still the optimal therapeutic approach and therefore standard of care. Due to the common multifocality and anatomic location of mucosal melanoma, surgery may be challenging or even impossible. In the case of localized but extensive disease, radiotherapy may be considered an alternative to surgery in order to achieve local tumor control. The role of sentinel lymph node biopsy is still controversially discussed, and there is a lack of clinical trials suggesting a benefit [15]. Hence, no recommendations regarding the prognostic value of sentinel lymph node biopsy can be made.

A variety of different therapeutic agents are available for the treatment of distant disease. If a $BRAF^{V600E}$ mutation is present, targeted therapy with a BRAF inhibitor in combination with a MEK inhibitor should be considered for first-line treatment, since response rates and PFS appear similar to those with BRAF-mutated cutaneous melanomas. In contrast to BRAF mutations, KIT mutations are more common in mucosal melanomas, and good response rates to the tyrosine kinase inhibitor imatinib have been described. These data, however, are exclusively valid for KIT-mutated mucosal melanoma and not for KIT-amplified tumors (RR 54 vs. 0%). In wild-type advanced mucosal melanomas, the use of immunooncological agents, especially nivolumab, provides valid data concerning ORR and PFS. However, no recommendations can be made regarding the duration of such therapies, nor are long-term data currently available.

In conclusion, there is a need to increase our understanding of the tumor biology and molecular mechanisms of oral mucosal melanoma in order to enhance and personalize therapeutic options. Currently, guidelines for treating this tumor are in development. Our case suggests that imatinib may be considered as a first-line treatment for both locally advanced and distant primary multifocal oral melanoma, for which surgery or radiotherapy of the primary tumor is impossible or associated with significant comorbidities or disfigurement. Treatment with imatinib achieved tumor control of both the primary tumor and the distant metastases for more than 1 year in our patient. Further studies are needed to prove a potential role of imatinib as first-line treatment for this challenging subtype of melanoma.

Statement of Ethics

Written informed consent was given by the patient. An ethics committee approval was not necessary because the patient was treated according to the tumor board recommendation and outside a clinical trial.

Disclosure Statement

The authors have no conflicts of interest to declare.

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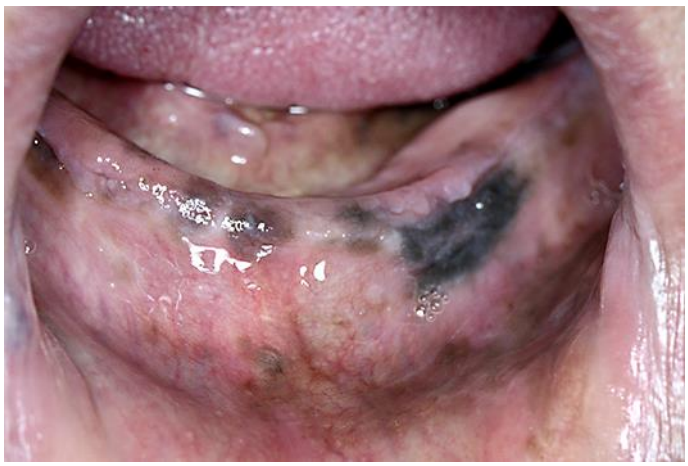

Fig. 1. Multiple, partially confluent, brown-to-black macules in the whole oral cavity also involving the base of the tongue and the hard palate.

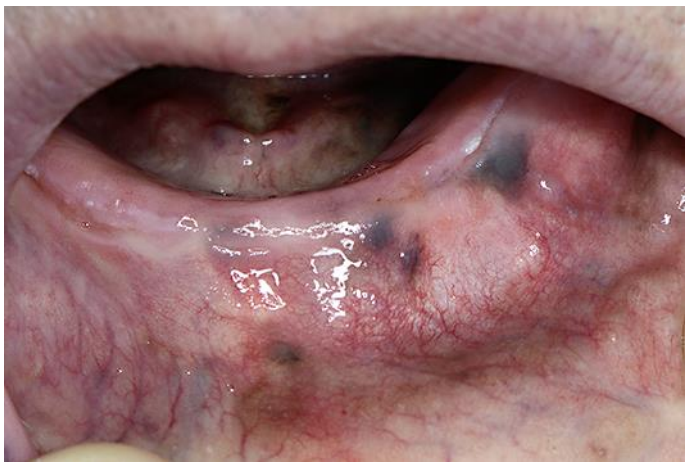

Fig. 2. Notable regression of the oral lesions 1 year after starting the treatment with imatinib at 400 mg once daily.