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Pembrolizumab for Gingival Melanoma: A Spectacular Response in a Challenging Case

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ABSTRACT

Malignant melanomas of the oral cavity are extremely rare tumors. The mandibular mucosa is the most frequent site for melanomas of the oral cavity. Although they are easy to detect due to their pigmentation and irregular shapes and contours, diagnosis is often delayed and only occurs in cases of ulceration or hemorrhage of the overlying epithelium. This late detection is the cause of poor prognosis. Mucosal Melanoma (MM) in general, and gingival melanoma in particular, represents a significant clinical challenge due to its aggressive nature and limited treatment options. Immunotherapy is a promising strategy for these melanomas, with a particular focus on immune checkpoint inhibitors, such as PD-1 inhibitors. We will report the case of a 70-year-old female patient who presented with gingival melanoma, and discuss through this case the diagnostic pitfalls and therapeutic options of this rare pathology.

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Introduction

Malignant melanoma of the oral cavity is an extremely rare tumor, accounting for less than 1% of all melanomas [1]. The mandibular mucosa is the most frequent site for oral cavity melanomas [2]. Clinically, they are relatively easy to diagnose due to their pigmentation and irregular shapes and borders. They are most often asymptomatic and are only detected when the overlying epithelium ulcerates or hemorrhages. Late detection can be the cause of the poor prognosis, with a five-year survival rate ranging from 15% to 38% [3].

Mucosal Melanoma (MM) represents a significant clinical challenge due to its aggressive nature and limited treatment options. In recent years, immunotherapy has emerged as a promising strategy for MM, with a particular focus on immune checkpoint inhibitors such as PD-1 and CTLA-4 inhibitors [4].

We will report the case of a 70-year-old female patient who experienced a rapid and complete response to Pembrolizumab.

Observation

A 70-year-old female, with a history of hypertension treated with medication, with no history of tobacco or alcohol use, and with no family history of cancer, presented with a blackish tumefaction of the mandibular gingiva that had been evolving for two months. An intraoral examination revealed a blackish, budding, pedunculated tumor, measuring 5 cm in diameter by 3 cm in width. The mass originated from the gingivo-mandibular symphyseal region, bled upon contact, obstructed the oral cavity, and invaded the anterior vestibule and the anterior floor of the mouth. Tongue mobility and oral opening were preserved. The clinical examination did not reveal any cervical adenopathy.

A facial CT scan was performed, which showed a heterogeneous, infiltrative, malignant soft tissue mass of the perimandibular and gingival tissues, with imprecise borders, measuring 40 x 42 x 24 mm. It was located medially and lateralized to the right in the symphyseal region, with erosion and mandibular lysis at that level. The mass was in contact with the muscles of the floor of the mouth without a clear cleavage plane. A biopsy with histological examination concluded a mature keratinizing squamous cell carcinoma of the gingiva. Surgical excision was performed, consisting of an interrupting segmental pelvi-mandibulectomy involving the symphyseal region, followed by the placement of a maxilla plate. No lymph node dissection was performed, and a feeding gastrostomy was also put in place.

Macroscopic examination of the resected specimen revealed a multilobulated, blackish, hemorrhagic tumor measuring 52 x 35 mm (Figure 1). Histological examination concluded a mixed tumor associating melanoma and verrucous carcinoma, with the

presence of tumor necrosis, a Breslow thickness of 7 mm, and a Clark and Mihm level IV (invasion of the reticular dermis). The deep margin was located 2 mm from the proliferation, and it was classified as pT4b.

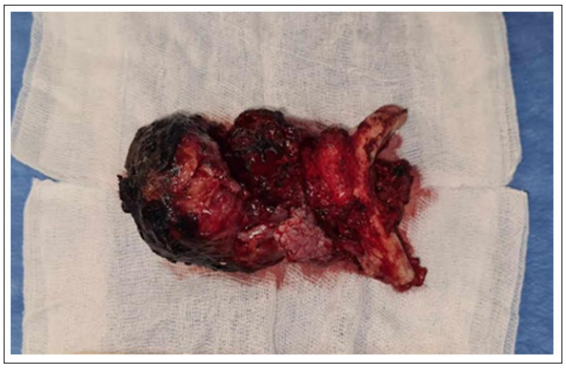

Figure 1: Macroscopic Appearance of the Surgical Resection Specimen (Photo Credit: Dr. Hadjer Guendouz)

Despite having clear resection margins, the patient experienced a massive recurrence just two weeks after surgery (Figure 2). The patient was taken back to the operating room, and a wide excision of the tumor was performed, but this time with infiltrated resection margins. Two weeks after the surgical procedure, the patient experienced a rapid progression (Figure 3A). A facial MRI performed at that time revealed a large, multilobulated gingivo-mandibular tumor, which was enhanced after Gadolinium injection and measured 72 mm in the anteroposterior axis, 61 mm in height, and 73 mm in transverse diameter. The presence of cervical lymphadenopathies was also noted, the largest of which was located in sector IIb and measured 40 x 32 mm.

Figure 2: Clinical Appearance of the First Local Recurrence (Photo Credit: Dr. Sarra Zeroual)

The case was discussed at a multidisciplinary team meeting, and we decided to put the patient on checkpoint inhibitors: Pembrolizumab at a dose of 200mg every 21 days. At the patient's check-up on day 8 after the first cycle, we already noted a partial clinical response (Figure 3B). Twenty-one days after the first cycle, the patient had a complete clinical response (Figure 3C). A follow-up scan performed after three cycles confirmed the complete tumor response. Furthermore, the patient did not experience any side effects from the immunotherapy.

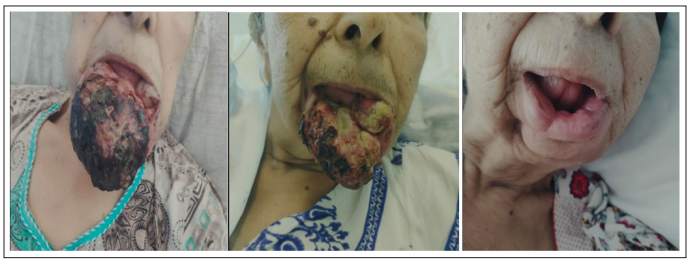

Figure 3: Clinical Evolution of the Gingival Melanoma After One Cycle of Pembrolizumab, from Left to Right: A: Day 0-B: Day 8-C: Day 21. (Photo Credit: Dr. Sarra Zeroual)

Discussion

Oral cavity malignant melanoma is an extremely rare tumor, accounting for less than 1% of all melanomas [1]. It preferentially affects the palate, uvula, and upper gingiva. Mandibular localization is the rarest, which makes the case we describe interesting, especially as it is the first to be reported in the literature in Algeria [2]. There is a male predominance, and the median age at diagnosis is 55 to 66 years [1,2]. In our case, the patient is a 70-year-old woman, which does not correspond to the cases described in the literature. Mucosal melanomas in general, and gingival melanomas in particular, are biologically distinct from cutaneous melanomas, and their causes are unknown. They often arise from pre-existing benign pigmented lesions. Unlike cutaneous melanomas, the carcinogenesis and etiology of gingival mucosal melanoma are still unknown. Several risk factors have been proposed, including human papillomavirus, chronic irritation from dentures, smoking, and chewing. However, no evidence has been provided to support these risk factors [3,5].

Oral malignant melanoma is generally painless. One-third of patients are asymptomatic at the time of diagnosis, and episodes of hemorrhage appear to be the main circumstance of discovery [6]. Oral melanomas have a wide variety of morphological and macroscopic clinical presentations, which can make clinical diagnosis very difficult [7]. The diagnosis is suspected in the presence of a non-homogeneous pigmented nodular lesion, which varies from dark brown to bluish-black, although it can be amelanotic. In 30% of cases, mucosal pigmentation precedes the appearance of the tumor by several months or even years. The surface of the lesion may be smooth or ulcerated, sometimes presenting with contact bleeding. Clinical examination must rule out an intraoral metastasis of a cutaneous melanoma [8-11].

The "ABCD" scoring system is used to differentiate malignant melanoma from benign pigmented lesions. These characteristics are as follows: A, Asymmetry; B, Border irregularity, often including a notch or irregular indentation; C, Color variations such as red, white, and blue; and D, Diameter greater than 0.6 mm [11]. Cervical lymphadenopathies are found in 25% of cases [8].

The differential diagnosis includes oral melanotic macule, post-inflammatory pigmentation, drug-induced melanosis, blue nevi, Addison's disease, amalgam tattoo, smoking-associated melanosis, drug-induced melanosis (antimalarials and minocycline), Peutz-Jeghers syndrome, Kaposi's sarcoma, and many other conditions with similar macroscopic characteristics [9,10,12].

Anatomopathological examination confirms the diagnosis and should ideally be performed on an excisional biopsy. It involves a malignant tumor proliferation of mucosal melanocytes. This is a rare subtype of melanoma that originates from melanocytes located in non-sun-exposed mucous membranes. Mucosal melanomas

share many histological characteristics with cutaneous melanomas, including three specific criteria: the appearance of the tumor cells (4 possible types: pseudo-epithelial, fusiform, undifferentiated, or mixed), the existence of junctional activity, and the presence of melanin in the tumor cells [13]. Histologically, mucosal melanoma is characterized by a proliferation of melanocytes within the mucosal epithelium. This proliferation manifests as isolated cells and nests, originating in the basal layer. Ulceration of the mucosal surface is a frequent observation. Pagetoid involvement of the surface epithelium may also be present [14,15]. It is important to note that mucosal melanoma can present a wide range of histological morphologies, including fusiform, pleomorphic, rhabdoid, plasmacytoid, and undifferentiated variants. The presence of prominent nucleoli and mitotic figures is commonly observed [14]. The pathology report must contain essential information for tumor classification and therapeutic decision-making, which we have summarized in Table 1, as well as optional information that we have summarized also in Table 1.

The major diagnostic challenge lies in the fact that approximately 50% of mucosal melanomas are amelanotic or have minimal pigmentation. This characteristic can lead to an overlap of morphological features with other small-cell or undifferentiated sinonasal tumors, making the differential diagnosis particularly complex. Immunohistochemistry is therefore essential to establish a definitive diagnosis, namely SOX10, S100, MelanA, and HMB45 [15,16].

Our patient had a specific characteristic, namely a mixed epithelial and melanotic tumor. The first biopsy had concluded that it was a squamous cell carcinoma because it only involved the epithelial component. However, given the specific clinical appearance of a malignant melanoma, a complementary immunohistochemical analysis could have corrected the diagnosis.

Table 1: Criteria Included in a Standard Pathology Report [16]

Mandatory Histopathological Characteristics to Include in the Pathology Report	Optional Histopathological Elements of the Pathology Report
Melanocytic nature	Histological subtype
Thickness in mm: Breslow	Cellular nature
Ulceration	Clark level
Lymphovascular invasion	Tumor-infiltrating lymphocytes (TILs)
Perineural invasion	Tumor growth phase
Status of resection margins	Associated nevus
Signs of regression	pT according to AJCC, 8th edition
Mitotic index (Number of mitoses/mm²)	

Prior to 2010, there was no dedicated staging system specifically adapted for mucosal melanomas of the head and neck, including oral melanomas. The 7th edition of the American Joint Committee on Cancer (AJCC) introduced a classification that recognized the aggressiveness of this entity, with all primary tumors being classified only as T3 or T4 [17,18]. It should be noted that this TNM staging system is the only one in AJCC7 that does not define T1 and T2 categories, which were omitted to reflect the overall poor prognosis of mucosal melanoma of the head and neck, even for small and superficial lesions (Table 2) [17-19].

Table 2: TNM Staging of Mucosal Melanomas, AJCC 7th Edition [19]

TNM Staging	Description
T3	Tumor limited to the mucosa and submucosa.
T4 T4a T4b	Involvement of the deep soft tissues, cartilage, bone, or overlying skin. Involvement of the skull base, brain or dura mater, cranial nerves (IX to XII), prevertebral space, carotid artery, mediastinum, and masticator space.
NX	Cannot be evaluated
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Presence of distant metastasis

Although several studies have advocated for its prognostic utility, a growing body of evidence now indicates that the AJCC7 staging fails to provide sufficient risk stratification in the evaluation of head and neck mucosal melanomas, and consequently, oral melanoma [19]. For this reason, the 8th edition omitted prognostic stage grouping for these entities [17-19].

In contrast to cutaneous melanoma, traditional prognostic factors such as Breslow thickness and ulceration are not applicable to mucosal melanoma. The identification of prognostic factors specific to MM is crucial for optimal clinical management. Additional studies are necessary to identify prognostic factors for tumors of mucosal origin. Histological, anatomical, and clinical factors have been studied in MM to predict outcomes (age, mitotic rate, cell type, ulceration); however, studies remain limited in this rare disease, preventing validation for clinical utility [20,21]. Metastatic disease remains the most important prognostic factor impacting patient survival, with a median survival of 24 months [20,21].

Due to the rarity of these tumors, treatment recommendations are often not based on exhaustive evidence but rather on small retrospective case series with a considerable potential for bias. Nevertheless, complete tumor resection with clear margins remains the cornerstone of treatment for patients with resectable head and neck mucosal melanomas. Guidelines in the United States [National Comprehensive Cancer Network (NCCN)] and Australia (Cancer Council Australia) currently recommend initial surgery for resectable AJCC stage T3 and T4a HNMMS [19,23]. Resection margins have a direct impact on overall survival, with a 21-fold increased risk of death associated with positive margins, as well as a significantly increased occurrence of distant metastases and a decrease in Overall Survival (OS) associated with the failure to achieve local control [24,25].

Adjuvant radiotherapy is used following a curative surgical procedure, or for advanced or recurrent disease after surgical resection with close or involved margins, or in patients with high-risk resected nodal disease [26,27]. The NCCN currently defines high-risk nodal disease as mucosal melanoma involving two or more lymph nodes with unfavorable features; any lymph node ≥ 3 cm in size; extranodal soft tissue extension; or recurrence in a nodal basin after a prior surgery [23].

Systemic treatment is reserved for unresectable or metastatic mucosal melanomas. While phase III clinical trials are not easy to implement due to the rarity of mucosal melanomas, data concerning the efficacy of immunotherapy have been reported in several studies and publications [28-34]. Currently, three immunotherapies are approved for the treatment of unresectable or metastatic mucosal melanoma: ipilimumab (a CTLA-4 inhibitor), nivolumab, and pembrolizumab (PD-1 inhibitors). The superior efficacy of combined checkpoint inhibitor therapy for mucosal melanoma has been confirmed in subsequent clinical trials and in a recent systematic review (n=1,262) [34-35].

Our patient showed a rapid and complete response to Pembrolizumab and remains in complete response after 6 months of treatment. After one year of treatment, the patient remains in complete response, with acceptable clinical and biological tolerance.

Conclusion

Mucosal melanoma is one of the most aggressive subtypes of melanoma and has a significantly worse prognosis than cutaneous melanoma, with a 5-year overall survival rate of less than 25%. The TNM classification does not accurately reflect the survival prognosis for these patients, and further studies are needed to identify risk factors specific to mucosal melanomas. Surgery remains the cornerstone of curative treatment, while immunotherapy has revolutionized the prognosis for inoperable and metastatic forms of the disease.

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