Primary Oral Melanoma – A Non-Surgical Approach to Treatment via Immunotherapy

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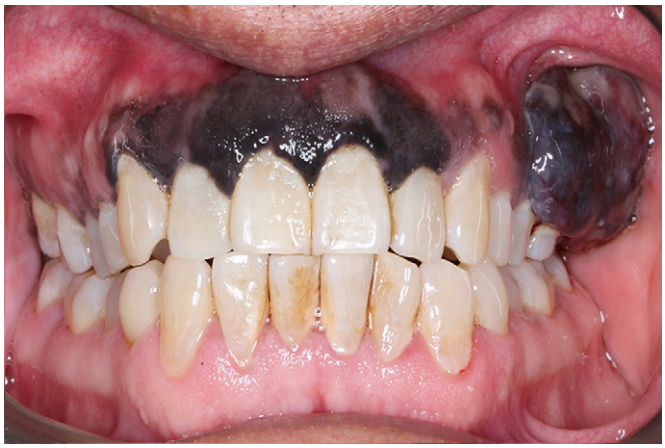

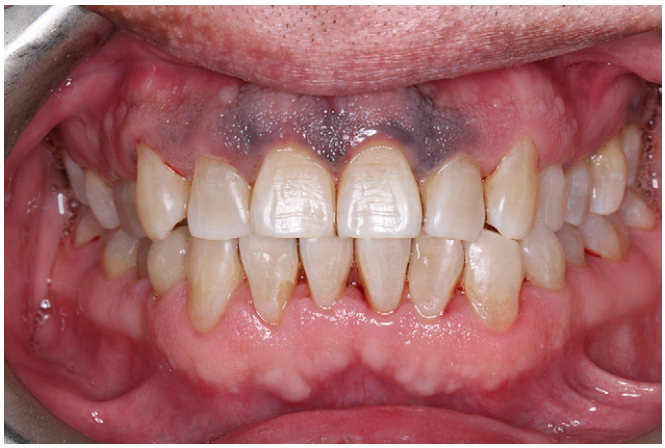

Introduction: Malignant melanoma is an aggressive form of cancer that commonly affects skin and rarely affects the oral cavity. With poorly understood risk factors and an often-asymptomatic presentation, oral melanoma is difficult to detect until advanced stages of disease. Treatment for oral melanomas has been primarily surgical, and survival rates have been low. However, in recent years, immunotherapy has shown much promise with increased patient survival.

Case Presentation: A 49-year-old male was referred by his primary dentist to a periodontal clinic for management of an alleged unresolved periodontal abscess. The patient had completed full-mouth scaling and root planing and consequently developed a large mass in the left posterior maxilla. Incisional biopsies were performed in multiple locations in the maxillary gingivae, and interpretation revealed atypical melanocytic proliferation and primary melanoma. After appropriate work-up, the patient was treated with two different immunotherapy agents: 1) ipilimumab and 2) pembrolizumab. Results after immunotherapy were favorable, and the tumor significantly decreased in size with no major adverse effects. The response was so strikingly positive that the need for surgical removal was almost eliminated. At the present time, it is unknown whether the patient will receive any surgical treatment barring a recurrence.

Conclusions: Oral mucosal pigmentation is a finding commonly encountered by dentists during clinical patient examinations. However, proper diagnosis of pigmented lesions, especially those associated with malignancy, requires investigations that go beyond clinical examination. *Clin Adv Periodontics* 2017;7:9-17.

Key Words: Biopsy; gingiva; immunotherapy; melanoma; periodontal abscess; pigmentation.

Background

Melanoma of the oral cavity is a very rare and particularly aggressive type of neoplasm. It represents <2% of all melanomas and only 1% to 2% of all head and neck neoplasias.[1] The average age of presentation in patients ranges from 22 to 83 years with a mean of 56 years of age.[1] Oral melanoma occurs mostly in men with a male-to-female incidence ratio of 2:1.[1] The hard palate is the most commonly affected site in the oral cavity, followed by gingiva and alveolar mucosa.[2]

Oral melanoma begins as a small, irregularly bordered, heterogeneously pigmented spot of a few millimeters in size and can arise *de novo* or from a preexisting pigmented lesion. Anywhere from 5% to 35% of the time, melanoma can present as an amelanotic form that can consist of pink, red, purple, or even normal pigmentation within the lesion.[3]

Melanomas are generally classified as cutaneous melanomas (91.2% of cases), ocular melanomas (5.3%), mucosal melanomas (1.3%), or melanomas of unknown origin (2.2%).[3] Melanomas of unknown origin are defined as melanoma resulting from metastasis without melanoma at the primary affected site.

To date, risk factors for oral melanomas remain unknown. No data today support the hypothesis that oral melanomas

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develop from traumatized nerves, chemical/thermal stimuli, smoking, alcohol, or poor oral hygiene.[3,4] Incidence of oral melanoma differs from that of cutaneous melanoma and has remained unchanged for the past 25 years.[5]

Initial development of oral melanoma is growth in a radial direction that progresses to rapid nodular growth. Radial growth is a horizontal spread along the basement membrane of adjacent mucosa.[4] Clinically, the tumor is initially asymptomatic and flat but with irregular margins. When the tumor reaches nodular or vertical growth, the lesion grows rapidly, establishes contacts with nerves and the lymphatic system, and can metastasize very quickly. Excision of the tumor in the initial radial phase has a much higher chance for a favorable outcome.[6]

Diagnosis requires biopsy and histologic examination with specific immunohistochemical markers such as S100 protein (S100), human melanoma black 5, and protein melan-A (Melan-A). Imaging studies and clinical examination of regional sentinel lymph nodes should be performed if a diagnosis of melanoma is made.

Currently, there are no guidelines for early detection of oral melanomas like those for cutaneous melanomas.[7] Clinical recognition of distinctive pigmentation, histologic evaluation, and use of Breslow depth method can help define type and extent of the lesion and patient prognosis.[8] Life expectancy at 5 years after diagnosis for oral melanoma ranges from 10% to 25% (median survival is 2 years).[4] At the time of diagnosis, 30% of patients present with positive lymph nodes. Survival rate at 5 years varies from 16.4%, for patients with affected lymph nodes, to 38.7% in patients with no lymph nodes affected.[4]

Treatment for oral melanomas has generally been surgical resection with wide margins. However, development and success of immunotherapeutic agents in improving outcomes for cutaneous melanomas has opened up new avenues for treatment of oral melanomas.[9]

Clinical Presentation

A Mexican male, aged 49 years, with no significant medical history presented for a periodontal evaluation at the Department of Periodontology and Implant Dentistry, New York University (NYU) College of Dentistry, New York, New York, in October 2014 with a referral to evaluate a "periodontal abscess" in the left posterior maxilla that appeared after scaling and root planing (SRP). The referral did not describe the initial clinical presentation of the lesion in the posterior maxilla, but radiographs revealed moderate horizontal bone loss and residual subgingival calculus in the area. The patient reported aches in the left posterior maxilla shortly after SRP, at which point the referral was made. The patient found clinical pain relief through chlorhexidine and non-steroidal anti-inflammatory drug use. It was not until about 3 months after SRP that he noticed a growing mass that became larger and darker. After noticing the large mass the patient subsequently fulfilled his referral and scheduled the appointment for evaluation. Also of note, the patient reported having mild pigmentation in the anterior maxillary gingiva for about 10 years but reports significant darkening of the area in the past 3 months prior to presentation to the periodontal evaluation in October 2014.

Upon intraoral clinical examination, a purple and black pedunculated mass ≈2 × 3 cm in size was evident in the attached gingiva and alveolar mucosa associated with the posterior left maxillary alveolus (Figs. 1 and 2). The mass was focally ulcerated and firm and painless upon palpation. A second diffuse, flat, black-pigmented lesion with irregular borders was also apparent on the anterior buccal maxillary gingiva extending from canine to canine and to the midpoint of the hard palate antero-posteriorly (Fig. 3). Areas of dark pigmentation from the second lesion extended to the attached gingiva associated with the posterior right maxilla on both the buccal and palatal aspects of the alveolus (Fig. 4). Extraoral examination of the patient revealed no other pigmented lesions or palpable lymphadenopathy.

Radiographs from prior to the referral were obtained. The patient's full-mouth series from January 2014 demonstrated findings of calculus and moderate horizontal bone loss in concordance with chronic periodontitis. A generalized interdental radiolucency was noted in the region spanning from the maxillary second premolar to the contralateral second premolar (Fig. 5). In the left maxillary quadrant, a small focal radiolucent area was identified in the interdental alveolar bone between the first and second premolar. During the referral appointment in October 2014, a new periapical radiograph was taken, and the updated image showed a diffuse radiolucency surrounding the root of the left maxillary first

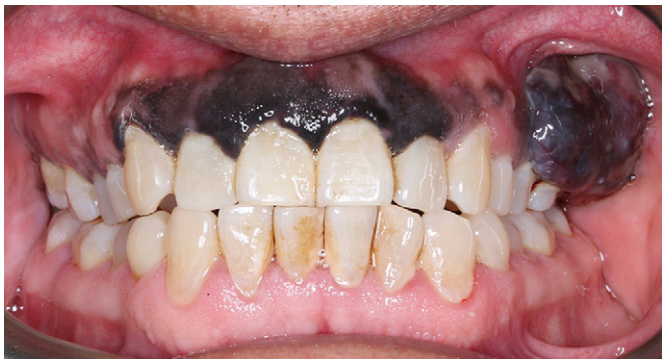

FIGURE 1 The patient presented with dark pigmented lesions in both the anterior and posterior maxilla (October 2014).

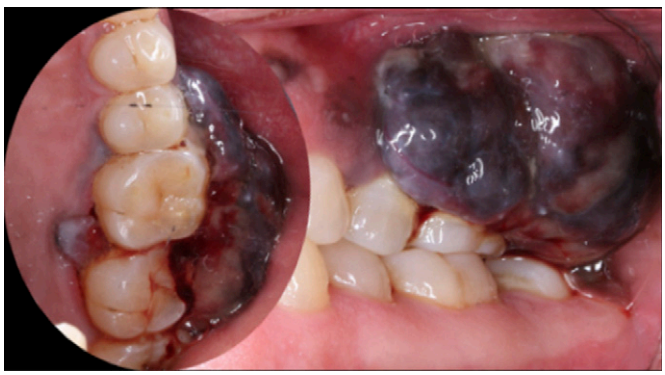

FIGURE 2 Exophytic mass in the left posterior maxilla that appeared after SRP.

premolar (Fig. 6). These changes in the alveolus did not affect tooth mobility or vitality.

After examination, the patient was referred to an oral pathologist (SS) for evaluation, biopsy, and microscopic examination. Due to the intense dark brown/black color of the lesions and their diffuse nature, the presumptive diagnosis at this point was oral mucosal melanoma. Vascular malformation was also considered as part of the differential diagnosis. Incisional biopsies were performed on both the flat, pigmented buccal gingiva of the anterior maxilla and the exophytic mass of the left posterior maxilla. Multiple biopsies were taken due to the differing clinical presentations of the two areas.

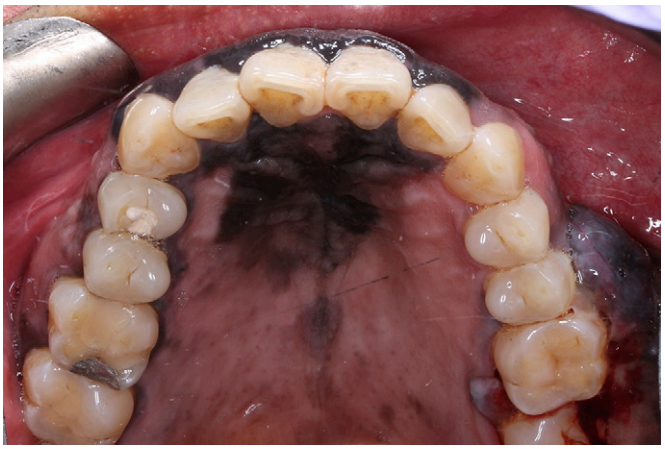

FIGURE 3 Diffuse, flat, black-pigmented lesion in the anterior maxilla extending onto the palate.

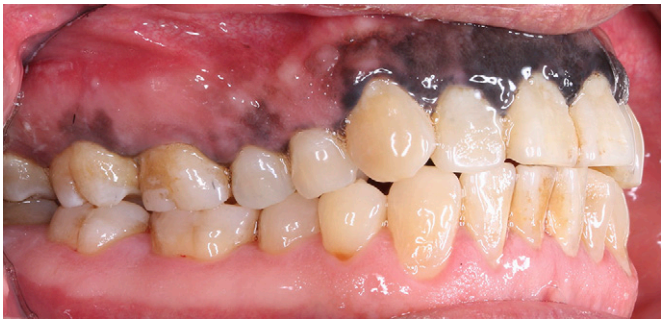

FIGURE 4 Areas of pigmentation extending to the right lateral maxilla.

The biopsy specimen of the buccal gingiva in the anterior maxilla showed hyperplastic epithelium with an atypical proliferation of melanocytes in the basal and parabasal cell layers (Fig. 7). Abundant melanin pigment was identified in the cytoplasm of the melanocytes (Fig. 8). Diagnosis of atypical melanocytic proliferation was made.

The second specimen, taken from the exophytic posterior buccal gingival mass, exhibited a proliferation of malignant melanocytes with a nested or lobular arrangement separated by thin fibrous septae (Fig. 9). Abundant intracellular melanin pigment was present. Tumor cells were pleomorphic with enlarged nuclei and prominent pink nucleoli. Abundant typical and atypical mitotic figures were identified (Fig. 10). Based on these findings, the diagnosis of melanoma was rendered. The specimen was sent for immunohistochemical staining to further confirm the diagnosis. S100 and Melan-A immunostains were positive, consistent with the diagnosis of melanoma.

Case Management and Clinical Outcomes

An interdisciplinary approach was implemented to deliver treatment. The patient was referred to an oral and maxillofacial surgeon (Brian L. Schmidt, Professor of Oral and Maxillofacial Surgery, NYU College of Dentistry) and an oncologist (Anna C. Pavlick, Professor and Co-Director of the Melanoma Program, NYU Langone Medical Center) specializing in melanomas. Further imaging studies of computed tomography and positron emission tomography scan

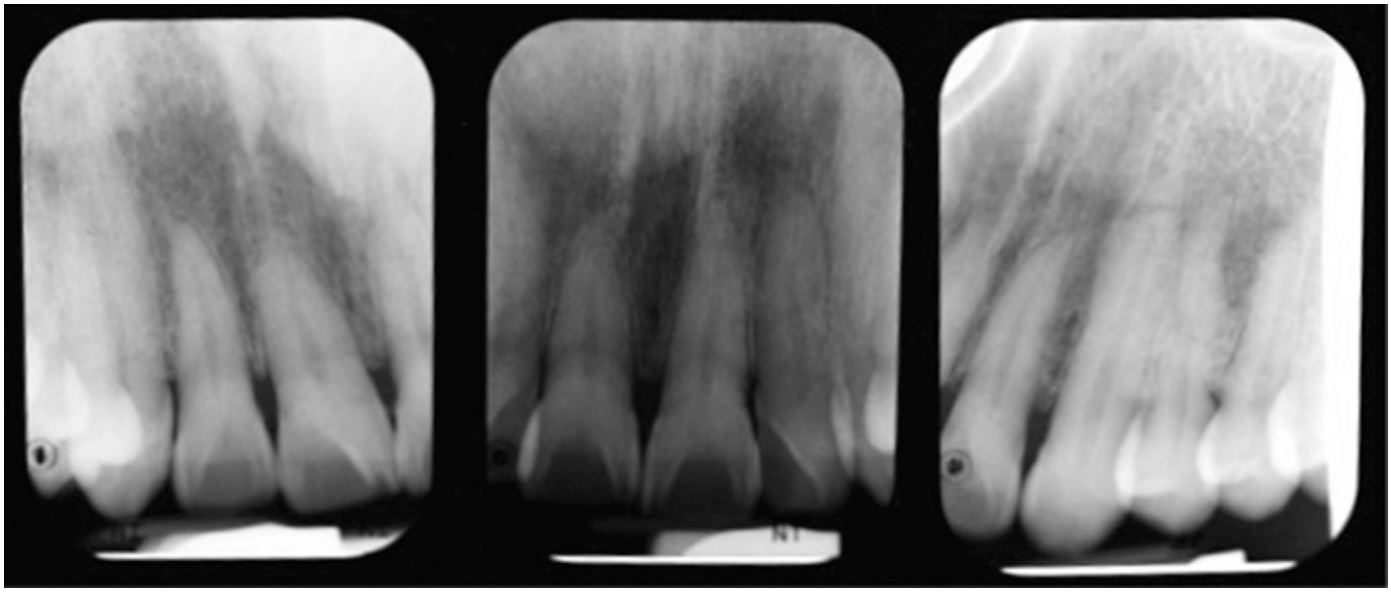

FIGURE 5 Periapical radiographs of anterior maxilla taken in January 2014 showing a generalized interdental radiolucency.

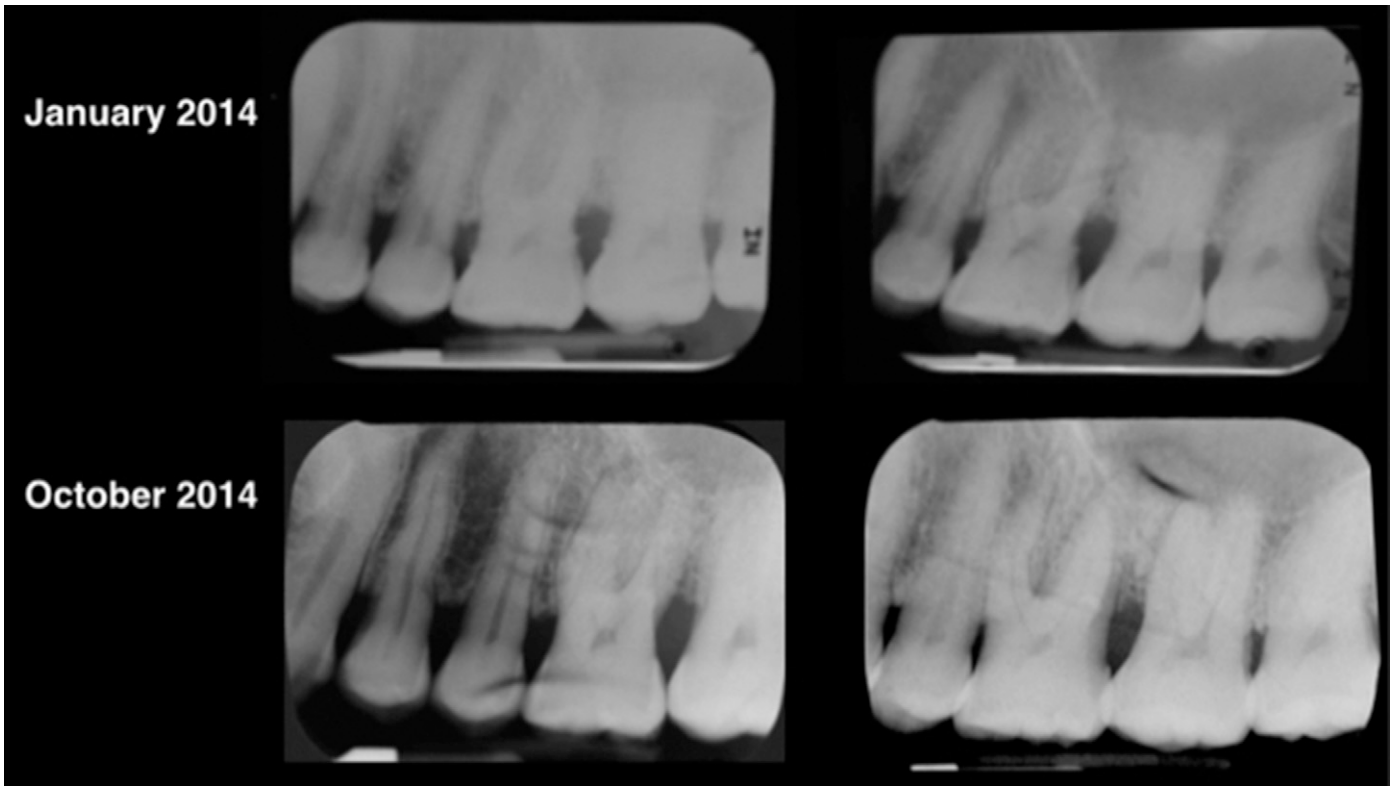

FIGURE 6 Radiolucency in the interdental alveolar bone before and after detection of the exophytic mass.

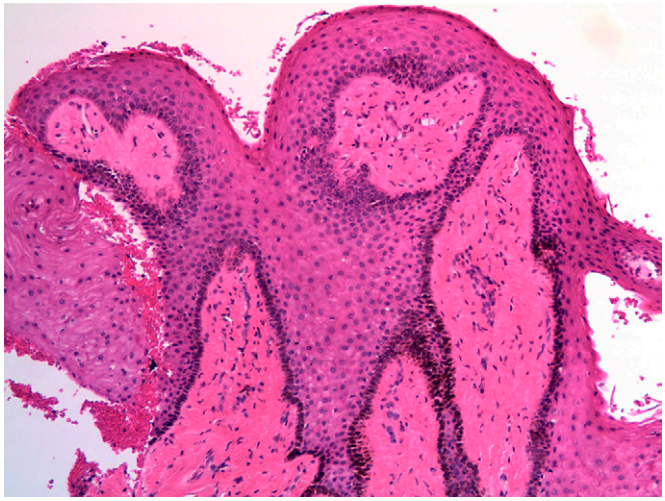

FIGURE 7 Epithelial hyperplasia with abundant melanin pigment in the basal and parabasal cell layers seen in the anterior maxillary gingiva (hematoxylin and eosin; original magnification ×10).

indicated the patient had three positive left neck lymph nodes (left level 1B and 2A) and required aggressive intervention. Scans revealed the tumor was too extensive for immediate surgical excision. BRAF, KIT, and NRAS mutation assays were ordered. Based on the results, the patient was placed on four 3-week cycles of ipilimumab (3mg/kg administered intravenously every 21 days), a relatively new targeted immunotherapy treatment for melanoma, to decrease tumor size prior to surgical treatment. The patient completed all four cycles of ipilimumab and tolerated the treatment well with no significant adverse effects, although he reported new headaches and dryness of eyes. The tumor responded positively to treatment and significantly decreased in size (Figs. 11 and 12).

Due to the excellent response to treatment another round of immunotherapy was prescribed. The patient was given two courses of pembrolizumab (2mg/kg administered intravenously every 21 days) and completed the course of four 3-week cycles. Although he responded well and the tumor continued to further decrease in size, one large lymph node of the original three persisted, showing only a modest decrease in size from 6 to 2 cm. To further combat the persistent node, the oncologist prescribed another four-dose round of the pembrolizumab immunotherapy. To date, he has completed a total of eight doses of pembrolizumab (Fig. 13), and the single persistent node is now 5 mm in size and considered resolved. The left posterior buccal gingival mass has completely resolved (Fig. 14). In the case of any recurrence or disease progression, the patient will be treated with surgical resection via hemimaxillectomy and selective neck dissection.

Discussion

Clinically, melanoma may have an appearance similar to that of a benign pigmented lesion. Differential diagnosis includes more common asymptomatic pigmented oral lesions such as amalgam tattoo, macule or nevus, melanoacanthoma, and focal melanosis.[2,10] Inflammatory pigmentation, racial pigmentation, and smokers melanosis may also be included in the differential diagnosis for more diffuse oral pigmentation. It is not until the advanced stages of disease that melanoma

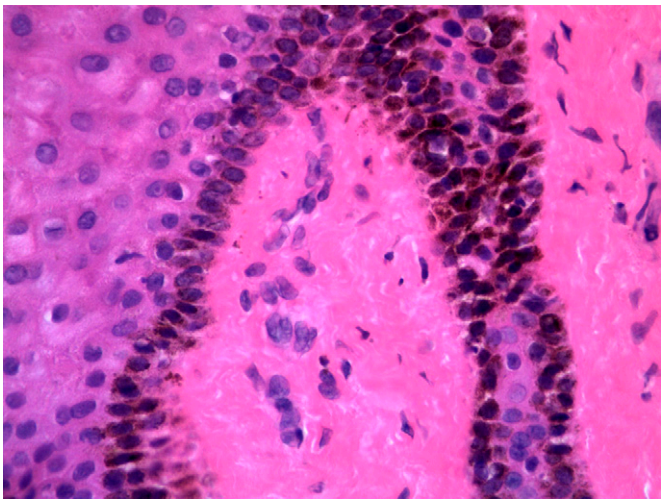

FIGURE 8 Higher-power view showing abundant melanin pigment in the cytoplasm of basal and parabasal epithelial cells (hematoxylin and eosin; original magnification ×40).

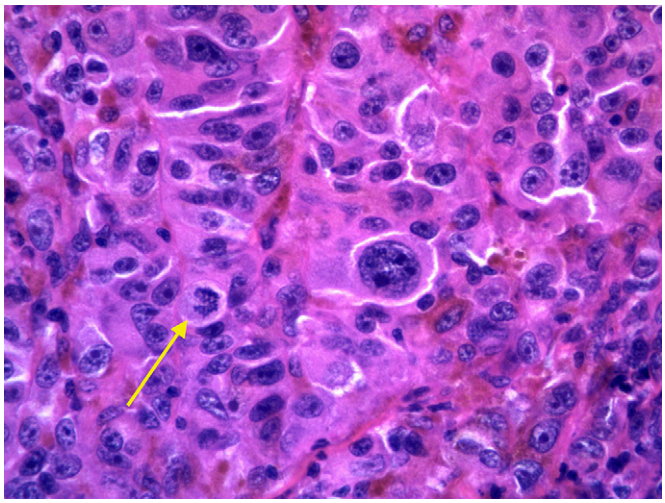

FIGURE 10 Higher-power view showing cellular atypia with enlarged nuclei and pleomorphism. An atypical mitotic figure is identified by the yellow arrow (hematoxylin and eosin; original magnification ×40).

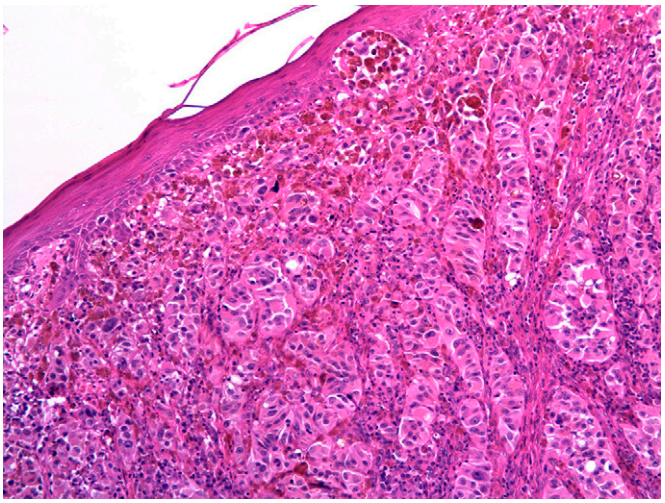

FIGURE 9 Nested or lobular arrangement of tumor cells with brown melanin pigment (hematoxylin and eosin; original magnification ×10).

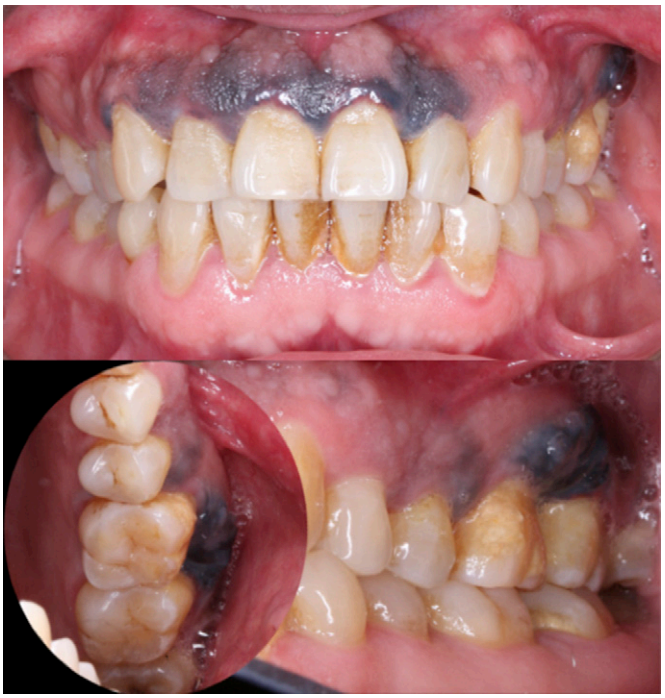

FIGURE 11 Reduced pigmentation and decrease in size of the posterior mass presentation after completion of ipilimumab therapy (April 2015).

develops clinical characteristics typical of oral malignant lesions. Common indicators of malignancy for pigmented lesions are asymmetry, border irregularities, color variations, overlying ulceration, and diameter >4 mm.[1]

Etiology of oral melanoma is essentially unknown. It has been proposed that tobacco use and chronic irritation or trauma play a role in pathogenesis but there is little evidence in the literature to support this claim. Most oral melanoma lesions arise *de novo,* but 30% of malignancies arise from existing oral pigmented lesions.[1,3]

In the current case, early diagnosis was difficult due to lack of symptoms or risk factors such as smoking or chronic trauma. The patient was of Hispanic origin, and racial pigmentation was considered but possibly favored too heavily, considering the skin complexion of the patient. The patient had periodontal disease and his report of the exophytic posterior maxillary gingival lesion arising abruptly after SRP seemed to point to a periodontal issue and abscess. Based on a literature search, no other case of an exophytic nodular oral melanoma arising after single-visit dental treatment (SRP) has been identified.

Biopsy of evolving, growing, and pigmented lesions is a prerequisite for proper diagnosis. Mimicry between different types of pigmented lesions and an extensive differential diagnosis make clinical diagnosis, especially in early stages, unreliable.[10] Oral mucosal melanoma can only be definitively identified by microscopic examination through presence of malignant melanocytes in the connective tissue.[11] Immunohistochemical staining with S100, Melan-A, and other similar markers is generally necessary as well and significantly assists in identification of poorly differentiated or non-pigmented melanoma lesions.

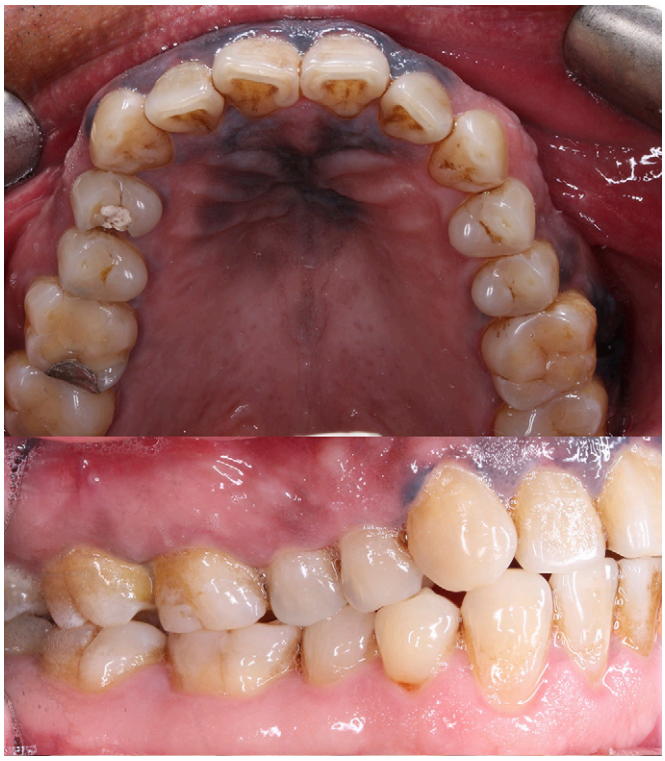

FIGURE 12 View of the hard palate and right maxilla after completion of ipilimumab therapy (April 2015).

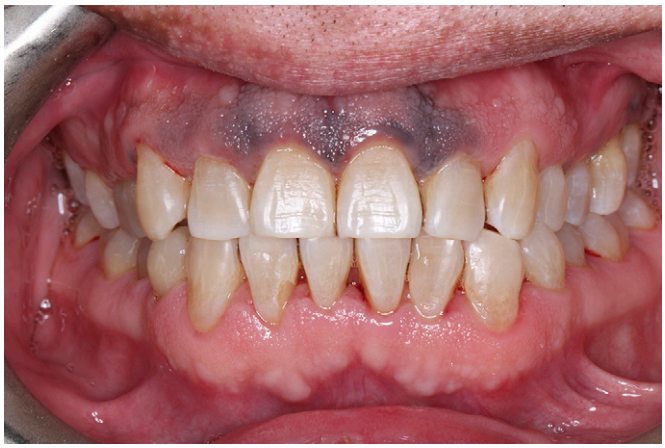

FIGURE 13 Further improvement after completion of pembrolizumab regimen (December 2015).

Biopsy site selection is also of critical importance. In this case, two incisional biopsies were taken. The biopsy from the posterior maxillary gingival mass showed melanoma. However, the biopsy taken from the anterior maxillary gingiva did not show a melanoma but only a melanocytic proliferation in basal and parabasal layers. If this was the only biopsy taken, the patient would not have received the correct diagnosis, and treatment would have been substantially delayed. The importance of taking multiple biopsies and including representative samples of varying areas of the lesion is highlighted by this case.

Unfortunately, there are no screening guidelines available to make patients and practitioners aware of predisposing risk factors for oral melanoma. Patients are at a greater disadvantage because they are unable to notice early lesions themselves due to the relative difficulty of self-detection in the oral cavity.

Traditionally, radical surgical therapy has been the main treatment option for melanoma patients. Chemotherapy and radiotherapy have been used as adjuncts.[3,5] Recently, new developments in immunotherapy and chemotherapy have increased treatment options available to patients with melanoma.[9,12-14] Many of these new options were initially developed for melanomas arising from the skin and have not been fully evaluated in treatment for mucosal melanomas. However, these therapies may result in more surgically conservative treatments, which may in turn offer greater quality of life in patients whose prognosis is poor.

Currently, two specific therapeutic strategies have significantly improved survival for patients with advanced melanoma: 1) immunotherapy with checkpoint inhibitors and 2) targeted therapies blocking *BRAF* and *MEK*. *BRAF* and *MEK* inhibitors are indicated for the approximately 40% to 50% of patients with *BRAF* V600 mutations, whereas immunotherapies are effective independently of *BRAF* mutational status.[12] The patient in this study tested negative for the *BRAF* V600 and *MEK* mutations, and therefore, checkpoint inhibitors such as ipilimumab and pembrolizumab were indicated.

The patient outlined in this case report completed a four-dose treatment with the immunotherapy agent ipilimumab, a monoclonal antibody that enhances antitumor immunity by blocking the negative regulatory function of cytotoxic T-lymphocyte antigen 4 (CTLA-4). Ipilimumab was approved by the US Food and Drug Administration (FDA) in 2011 and has since become a standard of care for patients with metastatic melanoma or surgically inoperable tumors. The drug has shown efficacy for cutaneous melanomas with overall improved survival rates and minimal toxicity.[13]

The patient completed eight doses of pembrolizumab after initial ipilimumab treatment. Pembrolizumab is a monoclonal antibody that targets the programmed cell death 1 receptor (PD-1). When activated T cells reach tumors, they can be functionally inactivated by engagement of PD-1 with its ligand, PD-L1, which is expressed in peripheral tissues and cancers. PD-1 functions as a checkpoint of the effector stage of the immune system, which is distinct from the role of CTLA-4 in limiting T-cell activation.[12] Pembrolizumab was approved by the FDA in September 2014 for use after ipilimumab treatment. A large Phase I trial led to response rates of 37% to 38% in patients with advanced melanoma and an overall response rate of 26% in patients who had progressive disease after treatment with ipilimumab.[15]

As previously stated, both ipilimumab and pembrolizumab function as checkpoint inhibitors and have revolutionized treatment of advanced melanoma. While CTLA-4 pathway inhibitors like ipilimumab modulate immune response at an early stage, PD-1 pathway inhibitors like pembrolizumab appear to have an impact at a later stage (Table 1). This mechanism of action suggests that dual

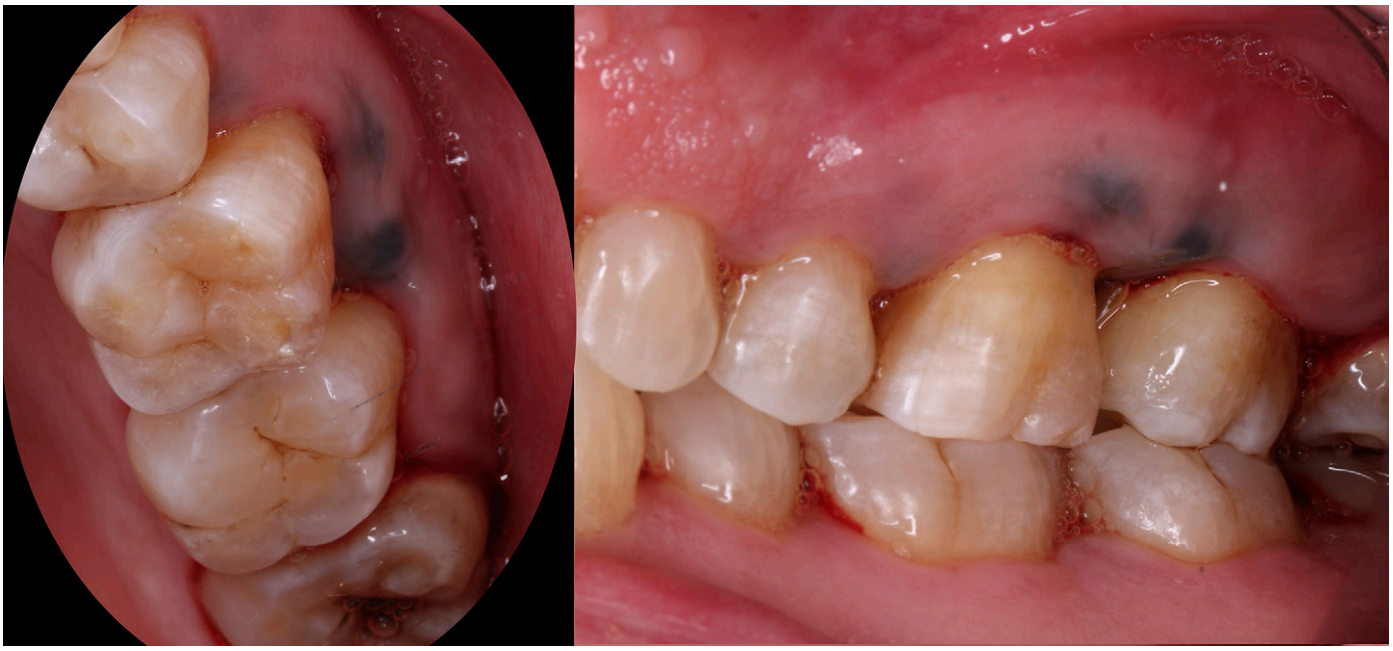

FIGURE 14 Almost complete resolution of the mass in the posterior maxilla (December 2015).

TABLE 1 Immunotherapy for Melanoma[9,14]

Type	Drugs	Mechanism	Indication
CTLA-4 checkpoint inhibitors	Ipilimumab Tremelimumab	Increase T-cell proliferation by inhibiting CTLA-4 mediated T-cell inhibition	Unresectable or metastatic melanoma
PD-1 checkpoint inhibitors	Pembrolizumab Pidilizumab Nivolumab	Inhibit PD-1-mediated T-cell inhibition via PD-L1 and PD-L2	Advanced melanoma that no longer responds to other drugs

checkpoint blockade with antiCTLA-4 and antiPD-1 antibodies could possibly show increased efficacy over single-drug therapy. The adverse effect profile of both drugs has been reported to be manageable and tolerable by most patients.[9] Combination therapy, however, showed an increased incidence of adverse effects but not increased toxicity over a 2-year period.[14] Clinical trials suggest that this combination therapy showed >80% reduction in tumor size in 36 weeks and a 2-year survival rate of 79%.[9] However, these statistics are for cutaneous melanomas, and immunotherapy medications remain largely untested for oral and other mucosal melanomas. Therefore, this case is unique, and future results will be of particular interest in treating other advanced oral melanomas with immunotherapy.

In this case report, the patient would have received a complete maxillectomy and radical neck dissection if surgery were the only treatment option for his advanced oral melanoma. His prognosis was not good, and his quality of life after extensive surgery would have been greatly decreased. However, the oncologist decided to attempt novel combination immunotherapy with ipilimumab and pembrolizumab in this extensive advanced oral melanoma case. The tumor has responded so well to these immunotherapy agents that presently surgery has been ruled out unless there is recurrence or progression. If this is the case, a hemimaxillectomy and a possible selective neck dissection of any involved nodes would be performed. The patient has tolerated the treatments well with no significant adverse reactions and remains in high spirits with a seemingly greatly improved prognosis. The complete non-surgical treatment and management of the advanced oral melanoma of the patient is a unique aspect of this case since oral melanomas are traditionally treated with only radical surgery.

Early detection and diagnosis is paramount to ensure the best possible outcome for patients with primary oral melanoma. Comprehensive oral exams at regular intervals and an understanding of the differential diagnosis and range of pigmented lesions of the oral cavity, from racial pigmentation to a harmless amalgam tattoo or macule to a life-threatening melanoma, are necessary prerequisites for achieving success in the identification, management, and treatment of oral neoplasms. More research is necessary to identify risk factors for oral melanoma to aid clinicians in distinguishing at-risk patients and detecting early lesions. Until then, practitioners should keep in mind the general guideline that all pigmented lesions of the palate and maxillary gingiva (high-risk sites for oral melanoma) should be biopsied for a definitive diagnosis.

Prognosis and survival rates of patients who are diagnosed with cutaneous melanomas have greatly improved with recent use of monoclonal antibody immunotherapy as an additional option to conventional radical surgery. This case shows great promise for the possibility of non-surgical treatment/management of oral melanomas through the use of these immunotherapy agents, thus preserving patient quality of life and greatly improving survival. ■

Summary

Why is this case new information?	■ This case presents, to the best of the authors' knowledge, a novel non-surgical approach to the treatment of advanced oral melanoma via immunotherapy.
What are the keys to successful management of this case?	■ Early diagnosis and rapid intervention are important in treatment of oral melanoma. Strict patient follow-up must be assured after initiating immunotherapy treatment to optimize clinical results.
What are the primary limitations to success in this case?	■ Size of the initial lesion and early metastasis can limit success. Further research is necessary to determine more specific limitations to the treatment of oral melanoma via immunotherapy.

Acknowledgments

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