CASE REPORT

Malignant melanoma of mandibular gingiva: A case report with literature review

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Abstract

The oral cavity is relatively a common site for pigmented lesions, most of them being benign, but rarely they may be malignant. Hence, dentist should keep the possibility of malignant melanoma in mind during any differential diagnosis of a pigmented lesions. The incidence of oral malignant melanoma is <1% of all melanomas and 1.6% of all head and neck malignancies. Although it accounts to be relatively a rare disease, it is a deadly one with a bad prognosis. We report a case of malignant melanoma for its rarity in mandibular gingiva and to emphasize the importance of early diagnosis and therapeutic intervention.

Keywords: Malignant melanoma, mandibular gingiva, prognosis

Introduction

Although oral malignant melanoma accounts to be relatively a rare disease, it is a deadly one with a very bad prognosis. The incidence of oral malignant melanoma is <1% of all melanomas and 1.6% of all head and neck malignancies.[1] It occurs due to uncontrolled growth of melanocytes in the basal layer of oral mucosa.[2] Its etiology is unknown. Possible etiological factors include: Use of tobacco, mechanical trauma, exposure to formaldehyde, and alcohol. Sometimes it can also occur on pre-existing long-term melanosis.[3]

It is having a higher incidence in yellows, blacks, Japanese, and Indians of Asia due to the more frequent finding of melanin pigmentation in oral mucosa of these races. It occurs between 30 and 90 years of age, with a higher incidence in the 6th decade.[2]

Symptoms for which a patient seeks an oral physician’s opinion is a rapid spreading discoloration of the oral mucosa. Some other uncommon features include tooth mobility, paresthesia, swelling, ulceration, hemorrhage, and pain in advanced cases.[4]

The clinical diagnostic criteria of melanoma is known as ABCDE criteria [Table 1].[4,5] Green et al. has stated few criteria for the diagnosis of primary oral melanoma which includes:

- Asymmetry (because of its uncontrolled growth pattern)
- Border irregularity (often with notching)
- Color variegation (which varies from shades of brown to black, white, red, and blue, depending on the amount and depth of melanin pigmentation)
- Diameter >6 mm (which is the diameter of a pencil eraser)
- Evolving (lesions that have changed with respect to size, shape, color, surface, or symptoms over time)

We report a case of primary malignant melanoma of the left mandibular posterior gingiva.

Case Report

A 30-year-old male patient presented with a blackish pigmentation on the left mandibular posterior region with the history of noticing it since 3 months. A dentist noticed it on routine checkup in a private clinic, otherwise not associated with pain or any other symptoms.

The lesion extended from the medial aspect of 33 to distal aspect of 38 measuring about 7 cm × 5 cm. The lesion was nodular with brownish-black pigmentation. The growth had an intact
surface with well-defined margins. The lesion was extending both buccally and linguually in marginal and attached gingival [Figure 1]. Orthopantamograph showed no significant bone pathology. Left submandibular lymphnode was palpable, 2 cm in size, mobile, firm in consistency, and non-tender. An incisional biopsy was taken from the buccal marginal and attached gingiva.

Microscopic examination of H and E stained sections showed dysplastic stratified squamous surface epithelium with proliferating atypical melanocytes in the radial and vertical pattern, along the basal cell layer and invading downward into the connective tissue [Figure 2]. Atypical cells were epithelioid in shape with vesiculated nuclei and prominent nucleoli. Varying degrees of nuclear pleomorphism and hyperchromatism were seen. Lesional cells showed fine melanin granules [Figure 3]. Mitotic figures were rare. A section bleached with hydrogen peroxide showed loss of brown melanin pigment [Figure 4]. In correlation with clinical features, the histopathological diagnosis of malignant melanoma of gingiva was made.

**Discussion**

Many pigmented lesions such as nevus, amalgam tattoo, melanotic macule, smoker’s melanosis, drug-induced pigmentation, systemic diseases, racial pigmentation and, of course, melanoma can occur in the oral cavity.[1] Although most of them are benign, clinicians must be able to differentiate between benign lesions and the rare, deadly malignancies like melanoma.

During embryologic development, melanocytes migrate from the neural crest into the epithelium of the skin, and they reside primarily in the basal layer. Similar to skin, the epithelial lining of the oral mucosa, normally contains melanocytes in its basal layer, which can evolve into melanoma as in the skin.[1]

The pathogenesis of oral melanomas is poorly understood. They are believed to arise either from nevus, pre-existing pigmented areas, Hutchinson’s premalignant lentigo or denovo 30% cases.[6] Some melanoma-associated antigens become expressed during transformation process from a benign
melanocytic nevus to melanoma; the majorities of these are related to the melanin production process and most are HLA-restricted.\(^{[6]}\) The loss of heterozygosity at 12p13 and p27KIP1 protein expression contributes to melanoma progression. Alterations in p53 gene have been identified in two-third of the cases. Evaluation of melanocyte-specific gene 1 and cytogenetic analysis appears to be helpful in understanding the pathogenesis of oral malignant melanoma.\(^{[3]}\)

Oral melanomas may present as painless, flat, black, or dark brown discoloration macules or nodules. Sometimes erythema or ulceration may also be seen. However, bony erosion is common only in the progressed disease.\(^{[5]}\) Pigmentation is absent in amelanotic melanomas. Oral melanoma initially is characterized by radial growth followed by vertical growth phase.\(^{[6]}\) Most of the melanomas are painless in their early stages; pain may be the later manifestation from ulceration, growth, or bleeding. Therefore, diagnosis is often unfortunately delayed.\(^{[2]}\) Since there was no pain in our case, could have caused a delay in seeking treatment.

Clinically, oral melanomas are classified into five types: Pigmented macular, pigmented nodular, non-pigmented nodular, pigmented mixed, and non-pigmented mixed.\(^{[6]}\) This case was clinically classified as pigmented nodular type. A biopsy is mandatory when a pigmented lesion cannot be confidently diagnosed as benign on clinical grounds, an incisional biopsy from the most suspicious part of the tumor in case of a large lesion and an excisional biopsy with 1 mm margin for small lesions is required. Exfoliative cytology and fine-needle aspiration of primary pigmented lesions is contraindicated. Cutting into a malignant neoplasm during an incisional biopsy or other invasive procedure could result in accidental dissemination of malignant cells within the adjacent tissues (seeding), lymphatic stream, or blood. This leads to the subsequent risk of, regional or distant metastasis or local recurrence. The most common sites of metastasis are bone, brain, liver, and lung.\(^{[6]}\) Bhullar et al. and Austin et al. stated that there was reduced survival rate in patients with melanoma who had incisional biopsies, but this was against the studies done by Lederman and Sober where they found no correlation in patient’s prognosis with incisional and excisional biopsies.\(^{[2]}\) If cervical lymphadenitis is present, FNAC should be performed to check for neoplastic cells.\(^{[4]}\)

A protocol has been highlighted for approaching a patient with oral pigmentation:

1. All oral pigmented lesions that could not be clinically diagnosed should be biopsied
2. Biopsy should be performed from the thickest and darkest region of the lesion
3. Pathologists should be provided with complete clinical information for biopsies
4. Follow-up of the patient should be done which includes thorough check up, chest X-ray, and clinical photographs.\(^{[4]}\)

Histologically, we find the proliferation of atypical melanocytes with a wide variety of shapes, such as spindle, plasmacytoid, epithelioid cells, and some clear cells.\(^{[5]}\) Atypical melanocytes are seen in the junction of epithelial and connective tissue, as well as invading into deeper connective tissue. Special techniques such as bleaching can also be useful for confirmative diagnosis.\(^{[4]}\) Oral malignant melanoma can be usually diagnosed with confidence on hematoxylin and eosin-stained sections. Immunohistochemical stains are of significant help in case of amelanotic melanoma where the pigment is completely absent.\(^{[2]}\) The useful diagnostic immunohistochemistry markers include: NKI/C-3, gp100 (HMB-45), Mart-1 (Melan-A), S-100 protein, tyrosinase, microphthalmia transcription factor, and vimentin.

A very important point in the management of malignant melanoma of the oral cavity is to exclude the possibility of it being a metastasis from cutaneous melanoma. This is because metastasis plays a large role in determining the goals and method of treatment.\(^{[7]}\) Primary oral melanoma commonly involves hard palate (32%) maxillary gingiva (16%), mandibular gingiva (7%), tongue (7%), buccal mucosa (7%), and upper and lower lip (7%). When the lesion is secondary or metastatic, they are more commonly present in tongue, parotid, and tonsils.\(^{[1]}\) In the histopathologic distinction, Billings et al. found that all metastatic lesions showed no evidence of junctional activity in the overlying mucosa and epidermal migration was also absent. This was in contrast to the primary lesion which had junctional activity and epidermal migration. Any suggested cutaneous or mucosal melanoma lesions elsewhere in the body should be absent for the diagnosis of primary oral mucosal melanoma. For our case, there was no history of melanoma-like lesion excision. We did not find any cutaneous lesions suggestive of malignant melanoma over other parts of the body. The histopathological findings revealed proliferating atypical melanocytes along the basal cell layer and invading downward into the connective tissue, suggesting that the tumor was a primary rather than a metastatic lesion.\(^{[3]}\)

There is no well-defined pathological and clinical classification for oral melanoma. Clark’s criteria of the cutaneous melanoma for the invasion level and the prognosis are not applicable to oral melanomas due to the lack of histological points of reference similar to the papillary and reticular dermis. But, few studies have compared oral melanomas with the cutaneous nodular melanoma and acral lentiginous melanoma.\(^{[3]}\)

The American Joint Committee on Cancer have not given the guidelines on the staging of oral malignant melanomas. However, the guideline usually followed is a clinical classification: Stage I - Clinically localized disease, Stage II - regional lymph node disease, and Stage III - distant disease.\(^{[2]}\)

According to Westbury, a clinical classification is as follows: 1 - only primary tumor present, and 2 - metastasis present, 2a - adjacent skin involved, 2b - adjacent lymph nodes involved, and 2ab - adjacent skin and lymph nodes involved.\(^{[2]}\)

Western Society of Teachers of Oral Pathology classify according to the histopathological pattern: (a) melanoma in situ, delimited to the epidermis and its junction with the connective tissue; (b) invasive melanomas, in which the neoplasia extends into the connective tissue, and (c) melanomas with a combined pattern between invasive and in situ.\(^{[3]}\)

Tumor node metastasis clinical staging system of good prognostic value can be followed, which divides into three stages. A recent histopathological micro staging for Stage I sub classifies
it into three levels. Stage I: Primary tumor present only (T any, N0, M0). Level I: Pure in situ melanoma without evidence of invasion or in situ melanoma with "micro invasion," Level II: Invasion up to the lamina propria, rand Level III: Deep skeletal tissue invasion into skeletal muscle, bone, or cartilage. Stage II: Tumor metastatic to regional lymph nodes (T any, N1, M0). Stage III: Tumor metastatic to distant sites (T any, N any, M1).\(^{[6]}\)

Controversies exist regarding the best treatment for oral malignant melanoma. Several studies state that radical resection of the primary lesion as the treatment of choice. A combination therapy of surgery, chemotherapy, radiotherapy, and immunotherapy should be considered.\(^{[6]}\) Immunological therapies have gained importance in recent years. Widely used cytokines are interleukin-2 and interferons.\(^{[7]}\)

Prognosis of this malignancy remains poor, despite the improvement in surgical techniques and use of new chemotherapeutic agents. Clinical stage at presentation is probably the most important factor in determining the prognosis. Liu et al. stated that thickness of the tumor, cervical lymph node metastasis, presence or absence of ulceration, and the anatomic sites are all independent risk factors.\(^{[2]}\)

The 5 years survival rate of primary oral melanoma is poor (15%) as compared to cutaneous melanoma (80%).

There can be several reasons for poor prognosis in primary oral melanoma:
1. Late diagnosis
2. Anatomic limitations making radical surgery difficult
3. Mucosal tumors show rapid invasion to deeper structures
4. Vascularity of oral mucous membrane
5. The mucous membrane is thinner than skin because of thinner lamina propria due to thin papillary dermis and absence of reticular dermis. Thus most mucosal melanomas progress quickly to vertical growth phase and gain access to the rich vascular and lymphatic network more quickly.\(^{[4]}\)

A careful oral examination and early biopsy will usually result in an early diagnosis thus improving the prognosis to a significant extent. In addition, public education about self-examination of the oral cavity with periodic oral checkup is important for early detection of such lesions.\(^{[4]}\) In our case, the prognosis would have been much better, if the patient had reported earlier when the lesion was flat and smaller in size; the 3 months delay resulted in the primary lesion being nodular and larger extending from the medial aspect of 33 to distal aspect of 38 measuring 7 cm × 5 cm.

**Conclusion**

The pigmented lesions in the oral cavity may show high potential growth and pose diagnostic challenges to a clinician. Hence, early biopsy and thorough clinical diagnostic workup of the pigmented lesion will lead to early diagnosis and therapeutic intervention, thereby improving the prognosis of the patients with oral malignant melanoma. The case is reported for its rarity in the mandibular gingiva.

**References**