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MALIGNANT MELANOMA OF PALATE - A RARE CASE REPORT

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ABSTRACT
Oral malignant melanoma (OMM) accounts for 8% of all oral malignancies. It is a rare aggressive neoplasm usually found on hard palate and gingiva. The etiology is unknown but tobacco and chronic irritation are suggested as probable causative factors. Over 30% of cases have been reported to arise from pre-existing pigmented lesions such as melanotic macules, smoker's melanosis, amalgam and graphite tattoos, racial pigmentation and vascular blood-related pigments. Though these lesions are biologically aggressive, they often go unnoticed since they are clinically asymptomatic in early stages and usually present merely as hyperpigmented patch on surface of oral mucosa. These lesions if diagnosed at early *in situ* stage are potentially curable and definitely have a better prognosis, but unfortunately as they are clinically asymptomatic, it results in delayed diagnosis thus making prognosis extremely poor. This case report discusses the rare malignancy, including clinical presentation, histopathological features, immunologic profile, management & prognosis. It highlights the importance of recognizing rare entities that may present in the jaws, the impact of the disease & its management.

KEYWORDS: Melanoma, Oral mucosa, Pigmentation, Prognosis, Recurrence.

INTRODUCTION
Melanoma is a malignant neoplasm of melanocytic origin that arises from benign melanocytic lesion or de novo from melanocytes within otherwise normal skin or mucosa.[1] Primary oral malignant melanoma is rare, accounting 0.2–8% of all melanomas.

Oral melanomas have male predilection compared to females with an average age of presentation in middle of sixth decade.[2]

Any mucosal site may be affected, however the palate represents the single most common site of involvement constituting 40% of all cases and maxillary gingiva is second most frequent site.[3] Oral melanomas have no distinctive clinical appearance, may be macular, plaque-like or mass forming, well-circumscribed or irregular and exhibit focal or diffuse areas of brown, blue, or black pigmentation.[2] This varied clinical presentation and being asymptomatic in the early stages, it frequently leads to misdiagnosis and delay in its management.

This case report highlights a rare case of oral melanoma of the right hard palate and explores the diagnosis & work up by Immunohistochemistry.

CASE REPORT
A 49 year old Asian male patient reported to the Department of Oral Medicine and Radiology with a chief complaint of oral ulceration on right side of roof of mouth since 3 months with difficulty in having foods and liquids. The ulcer was pin head in size which gradually increased to present size, which bleeds easily on touch. At the time of presentation, the patient did not report any systemic symptoms, had no history of fever or weight loss. The patient is a chronic smoker & alcoholic. No abnormalities were detected on general physical examination and the TMJ examination.

On Extra oral examination, a solitary right submandibular lymph node was enlarged, 1x3 cm in size, firm to hard in consistency, mobile, non tender.

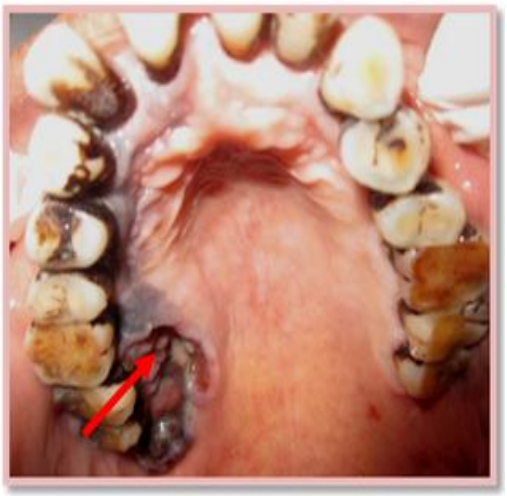

Figure 1 Ulceration on right side of palate.

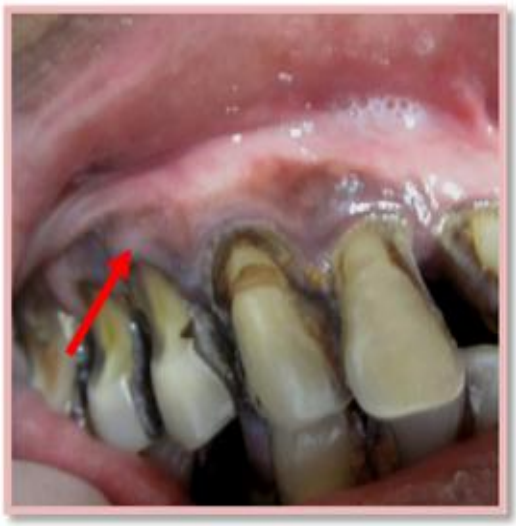

Figure 2 Diffuse pigmentation on maxillary buccal gingiva.

Intra oral examination revealed (Figure 1) an endophytic ulcerative lesion present on right side of palate extending from distal aspect of maxillary first molar to distal aspect of maxillary third molar measuring about 3cm x 2cm, with everted edges. There was diffuse brownish black streaking of pigmentation on lateral margin of the ulcer and on marginal and attached gingiva both buccally and palatally extending from maxillary lateral incisor to the maxillary first molar (Figure 2). On palpation, inspectory findings were confirmed and the ulcer was non tender with indurated margins & rolled out borders. The ulcer was bleeding on slight provocation. No teeth in the quadrant were decayed and the overall periodontal status of the patient was poor. Based on the history and clinical presentation of an ulcerative lesion with streaking of pigmentation at the lateral borders and indurated margins, a provisional diagnosis of Malignant melanoma of right palate was given. Other lesions like melanocytic hyperplasia, squamous cell carcinoma were considered as differential diagnosis.

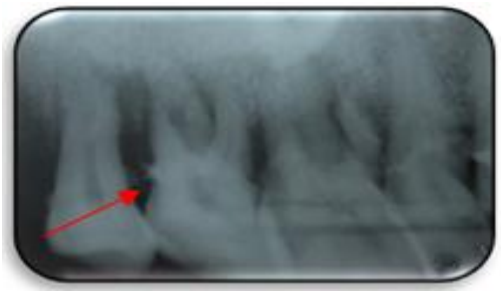

Figure 3 Intraoral periapical radiograph shows severe bone loss irt 15, 16, 17 with remnants of trabeculae in the interdental space between 17, 18.

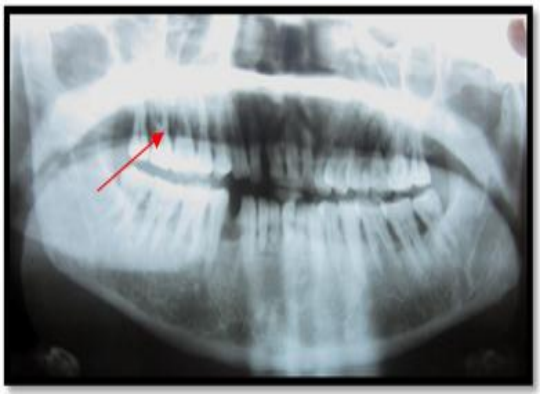

Figure 4 Orthopantomograph shows severe generalized bone loss extending from 13 to 18.

Intraoral periapical radiograph (Figure 3) shows severe bone loss irt 15,16,17,18 with remnants of trabeculae in the interdental space between 17,18. Orthopantomograph, (Figure 4) shows generalized bone loss with respect to 13-18. On computed Tomography, (Figure 5) erosion of alveolar bone in right posterior maxilla was noted. The routine blood examinations were within normal limits. The patient was negative for human immunodeficiency virus (HIV). The patient was advised for incision biopsy of the ulcerative lesion.

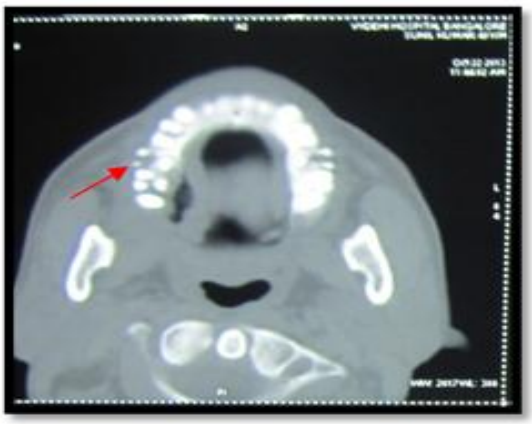

Figure 5 Computed Tomography shows erosion of alveolar bone in right posterior maxilla

Incisional biopsy of ulcer was performed and histopathologic examination (H&E) revealed (Figure 6) tumor composed of melanotic cells arranged in cords and

trabeculae, these cells were pleomorphic with moderate amount of eosinophilic granular cytoplasm and high nuclear cytoplasmic ratio, their nuclei were pleomorphic with coarsely granular chromatin and macronuclei. Few melanotic cells show cytoplasmic dark brown pigment granules and stroma shows inflammatory infiltrate. The features were suggestive of Malignant melanoma.

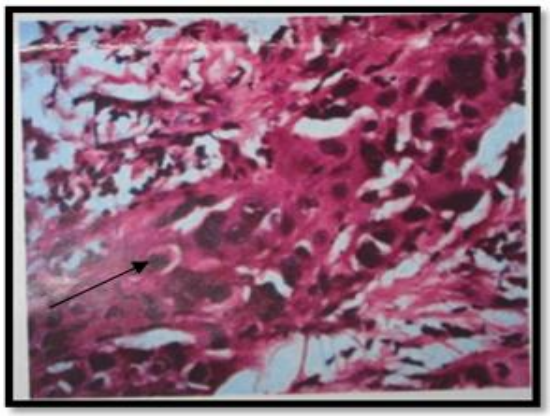

Figure 6 On H & E staining (40X) revealed tumor cells arranged in cords & trabeculae with macronuclei.

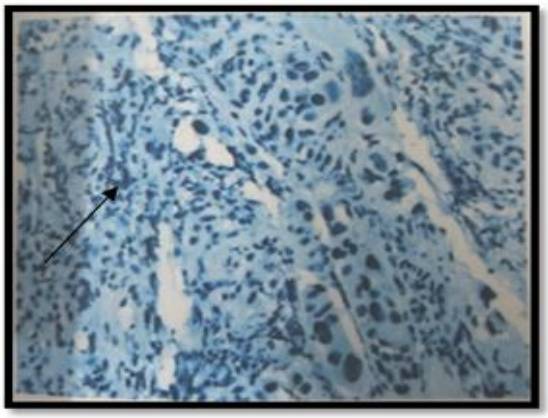

Figure 7 On Immunohistochemistry 90% of melanotic cells positive for HMB45 were evident

Further to confirm the malignant melanoma, Immunohistochemical examination of the specimen revealed 90% of melanotic tumor cells were positive for HMB 45 (Figure 7). Thus based on the immunologic profile final diagnosis of malignant melanoma was given. To rule out metastasis, a chest radiograph, USG of whole abdomen, whole body MRI was done which revealed no evidence of lesion elsewhere. Patient was referred to oncology department for further management. Patient was treated by right hemimaxillectomy with obturator placement and was given radiotherapy and the patient is still under follow up.

Table 1 Clinical staging system for oral malignant melanoma with histopathologic microstaging [2]

Stages	Extension of lesion
I	Primary tumor present only (T any N0M0) Level I: Pure *in situ* melanoma without evidence of invasion or melanoma with "microinvasion" Level II: Invasion up to the lamina propria Level III: Deep skeletal tissue invasion into skeletal muscle, bone, or cartilage
II	Tumor metastatic to regional lymph nodes (T any N1M0)
III	Tumor metastatic to distant sites (T any N any M1)

Staging by Prasad *et al*[2]

DISCUSSION

Oral melanoma is a very rare, highly malignant and aggressive neoplasm frequent in countries like Japan, Uganda and India. In the past 30–40 years, incidence has risen markedly and continues to increase in the USA, Asia and Europe, the main prevalence of melanomas was among whites (22–32% of all melanomas).[4] The first case of oral melanoma was reported in 1885 in the

English literature.[5] Indian studies show between 20.41% and 34.4% of all melanomas at mucosal surface and up to 16% of these tumors are intraoral.[4]

The highest incidence of malignant melanoma is in fifth decade of life (40-70 years). Males appear to be more often affected than females, in ratio of 2:1.[4] It occurs most frequently in the maxilla, with palate as common site (32%); maxillary gingiva is the second most frequent site of incidence(16%).[2] Cigarette smoking, denture irritation and alcohol consumption are some of the suggested risk factors, but their correlation is still unsubstantiated. Tobacco and formaldehyde exposure have also been suggested as causative for intraoral melanomas.[6]

A genetic background for the development of oral melanoma has also been proposed. Melanoma-prone families have high incidence of germline mutations in the tumor suppressor genes, *CDKNA2/p16INK4a* (Cyclin dependent kinase inhibitor 2A/P16) or less commonly *CDK4* (Cyclin dependent kinase 4) also frequently exhibit mutations in the *BRAF* (v-Raf murine sarcoma viral oncogene homologue B1), *HRAS* (Harvey Rat sarcoma gene) and *NRAS* (Neuroblastoma Rat sarcoma gene) proto-oncogenes. Other molecular findings, include *MC1R* (Melanocortico 1 receptor) polymorphisms and alterations or loss of PTEN (Phosphatase and tensin homologue gene) function, have been described.[3]

Oral melanoma may appear in various forms as pigmented macule, pigmented nodule, or large pigmented exophytic lesion or an amelanotic variant of any of the three forms. Lopez *et al*. identified 5 types of oral malignant melanoma (OMM) on the basis of clinical appearance: Pigmented nodular, Non‑pigmented nodular, Pigmented macular, Pigmented mixed and non‑pigmented mixed.[6] According to this our case can be identified as pigmented mixed type of OMM.

The clinical coloration of oral melanomas has a wide range, which can appear as black, gray, purple and even reddish. While some lesions are uniform in color, others exhibit marked variations. The tumors are asymmetric, irregular in outline and occasionally multiple. The surface architecture ranges from macular to ulcerated and nodular.[7] Additional signs and symptoms that may be associated with oral melanoma are nonspecific and similar to those observed with other malignancies. Ulceration, pain, tooth mobility or spontaneous exfoliation, root resorption, bone loss and paresthesia/anesthesia may be evident. However, in some patients, the tumors may be completely asymptomatic.[3] Metastasis to regional lymph nodes can occur.

The features of Melanoma are referred to as the acronym "ABCDs" i.e. the lesion will be Asymmetrical, Borders irregular, Color variation, Diameter enlargement and Darkening.[8]

Differential diagnosis includes other forms of pigmented diseases like Amalgam tattoo, oral melanotic macule, Melanocytic hyperplasia, Nevus (junctional or compound), Focal hemosiderin deposit, Local patch of melanoplakia, Melanocytic nevus and Melanoacanthoma.[9]

Radiographic features of ill defined irregular bone destruction are evident if melanoma involves the bone. Computed Tomography helps to determine extent of the tumor, where as contrast enhancement is used to determine extent of the melanoma, whether local, regional, or lymph node metastasis is present.[12] Magnetic resonance imaging is used to diagnose melanoma in soft tissue. On T1-weighted images, melanomas are hypointense, on T2-weighted images, melanomas are hyperintense.[1] CT and MRI studies should be undertaken to explore regional metastases to the submandibular and cervical lymph nodes.[4]

Histopathology confirms the diagnosis of oral malignant melanoma. The histologic appearance of the tumor is an invasive pattern of growth, with tumor cells often appearing as densely packed epithelioid or sometimes sarcomatoid cells with eosinophilic cytoplasm. Varying degrees of cellular pleomorphism are seen throughout specimen. Special stains (Fontana silver stain and Prussian blue stain) are accurate in only about 75% of the cases.[2] The immunologic markers will help in detecting the cell of origin. Demonstration of the neuronal specific S-100 protein is a useful diagnostic indicator for amelanotic melanoma. Application of monoclonal antibody techniques HMB-45 and Mart-1 (Melan A) confirms the immunohistochemical diagnosis of melanotic melanoma. Ultrastructural examination of melanoma by electron microscopy shows presence of pre-melanosomes and melanosomes.[2]

Clinical & histopathologic microstaging will be helpful in treatment planning. Surgery is considered to be the primary treatment for malignant melanoma and since oral melanomas have a grave prognosis, radiotherapy and chemotherapy serve as adjuvants.[10] Radiotherapy is administered especially in the early stages of Melanoma using 15MeV linear accelerator. Normally a dose of 62 to 68 Gy is given.[10] Chemotherapy can be given using: Daccarbazine – DTIC & INF α-2b, DAV protocol- D-Dimethyltriazeno-Imidazole-Carboxamide, A- ACNU (Nimustine Hydrochloride),V- Vincristine.[10]

Immunoregulatory monoclonal antibodies Ipilimumab, Agonistic antibodies anti CD137 (4-1BB), v-Raf murine sarcoma viral oncogene homologue B1 (BRAF) inhibitors, Non-selective BRAF inhibitors Sorafenib, Selective BRAF inhibitors Vemurafenib. Anti-B-cell lymphoma (BCL)2 antisense oligonucleotide, Proteasome inhibitors Bortezomib are chemotherapeutic agents tried recently.[11]

Recent and innovative treatment modality includes 'immunotherapy'using OK 432 and interferon α-2[10] A new vaccine: to treat advanced melanoma, called Onco VEX (Talimogene laherparepvec), an oncolytic virus- a reprogrammed virus converted into a cancer-fighting agent that attacks cancer and leaves healthy cells alone has recently shown positive results in 3rd phase of study.[12]

Surgical treatment includes Electrodesiccation and cryosurgery for early, superficial, palatal lesions. Ablative surgery with tumor-free margins remains treatment of choice. Early surgical intervention when detected enhances survival. Multimodal therapy is proven effective in treatment of oral mucosal melanoma. Surgical lymph node harvesting depends on identification of positive nodes at clinical or imaging examination.[12]

Prognosis of oral lesions is worse than skin lesions. A more likely reason for this is late presentation of patients with locally advanced disease. The rich vascularity and lymphatic drainage of the mouth favors earlier metastatic spread to regional lymph nodes and to distant sites such as lungs and vertebral column.[2] Regarding our case, the patient was treated by right hemimaxillectomy with obturator placement and was given radiotherapy and the patient is still under follow up**.**

CONCLUSION

Malignant melanomas clinically may be silent and asymptomatic, leading to delay in diagnosis. A careful clinical evaluation that is supported by radiologic, histopathologic and Immunohistochemical studies can assist in diagnosis. We as oral diagnosticians should lay emphasis reiterate on importance of maintaining a high index of suspicion and early detection & diagnosis for any pigmented lesions, especially if they occur in high risk sites like palate or gingival.

Early & accurate diagnosis followed by aggressive management is crucial & any delay in management worsens the prognosis.

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