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IP Journal of Diagnostic Pathology and Oncology

Journal homepage: <https://www.jdpo.org/>

## Case Report

# An unusual presentation of oral malignant melanoma: Disguising as a periapical granuloma

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### ARTICLE INFO

#### Article history:

Received 02-04-2022

Accepted 19-04-2022

Available online 19-05-2022

#### Keywords:

Melanocytes

Immunohistochemistry

Diagnosis

### ABSTRACT

The present case report comprises of an unusual presentation of oral malignant melanoma which occurred in the furcation area of maxillary right first molar. A clinician may not suspect a malignant neoplasm and the histopathological examination of the tissue may be missed out in such cases. Without any obvious clinical or radiological features, the lesion mimicked a periapical granuloma. The diagnosis was achieved after a thorough histopathological examination and extensive immunohistochemistry panel to rule out other similar histopathological entities.

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## 1. Introduction

The melanin pigment-producing cells, called as ‘melanocytes’, are generally present in the basal layer of the dermal epithelium and also in the mucosal epithelium. They are derivatives of the neural crest and account for brownish coloration of the skin or mucosa. A malignant neoplasm deriving from these cells is termed as ‘malignant melanoma’. It may arise from the melanocytes present in the skin, mucosa or internal organs (autochthonous).<sup>1</sup>

Majority of cases of melanoma are cutaneous, while only 0.4-18% cases occur in the mucosa.<sup>2</sup> The foremost case of malignant melanoma occurring in the oral cavity was described by Weber in 1859. Gingiva and palate are the most common sites of occurrence of oral malignant melanomas (OMM), followed by labial and buccal mucosae, and the tongue.<sup>3</sup>

Histopathologically, it may display a varied picture resembling numerous other entities, exclusion of which requires a carefully planned approach for investigations.

The tumor is highly aggressive and displays a marked tendency for local as well as distant metastases.<sup>3</sup> Therefore, it is of great importance to diagnose cases of melanoma early for an improved prognosis.

Herein, we report a case of OMM that displayed a very unusual presentation, involving the furcation area of a maxillary molar. Our case also demonstrates a careful step-by-step evaluation of biomarkers to exclude the histopathologically similar entities before a confirmatory diagnosis.

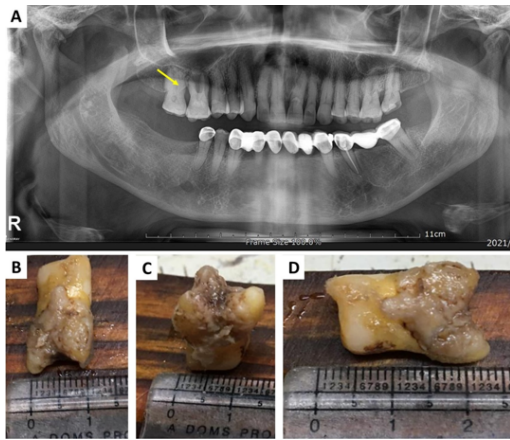
## 2. Case Report

A 63-year-old female complained of pain in the upper right back region of the jaw since three months. A history of chronic periodontitis was elicited from the referring dentist. The patient was also operated for a brain tumor few years back, the details of which were not available at present. She did not have any tobacco-related or parafunctional habits.

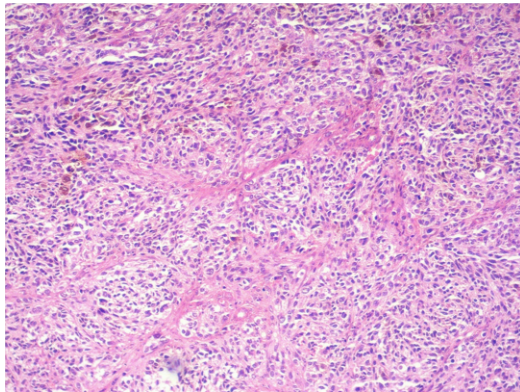
On intra-oral examination, no significant findings could be observed in the area of chief complaint, except for grade II mobility with the maxillary right second premolar, and

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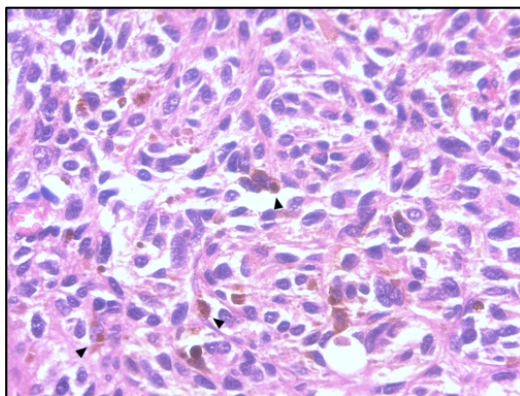
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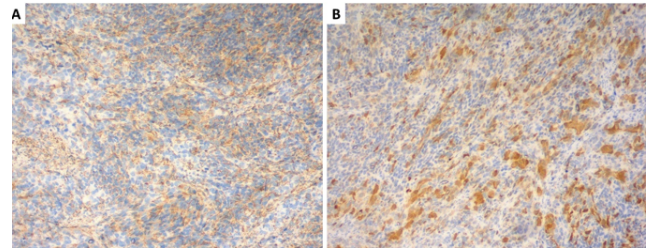
**Fig. 1:** A: Orthopantomogram exhibiting moderate horizontal and angular bone loss in the maxillary right premolar-molar region; B-D: Gross specimen showing a grayish to brownish mass adherent to the extracted first molar



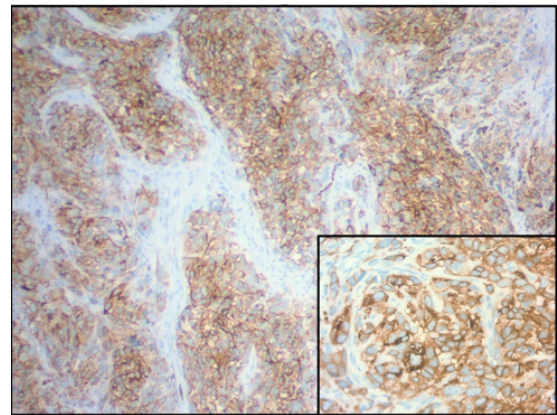
**Fig. 2:** Nests and fascicles of round to epithelioid cells separated by fibrous septae. (H and E, original magnification X100)



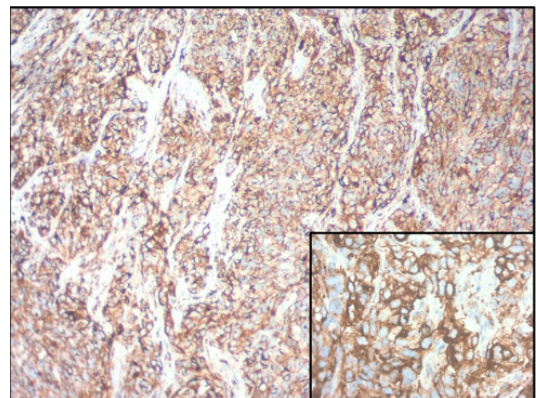
**Fig. 3:** High power view showing cells with 'peppered moth' nuclei. Arrowheads denote cells with coarse pigments. (H and E, original magnification X400)



**Fig. 4:** A: Expression of vimentin of moderate intensity observed diffusely throughout the tumor cells and stromal elements (original magnification X100); B: 40-50% of tumor cells exhibiting intense cytoplasmic immunoreexpression of S-100 (original magnification X100)



**Fig. 5:** Intense cytoplasmic immunoreexpression of Melan-A noted diffusely in the tumor cells. (original magnification X100; Inset: original magnification X400)



**Fig. 6:** Intense membranous immunoreexpression of HMB-45 noted diffusely in the tumor cells. (original magnification X100; Inset: original magnification X400)

the first and second molars. Additionally, the maxillary first molar was tender on percussion. The gingiva associated with the tooth was also inflamed, although not much calculus was evident surrounding the tooth.

The orthopantomogram did not exhibit any significant abnormality except for moderate horizontal and angular bone loss in the premolar-molar region (Figure 1A). The maxillary first molar being highly mobile, a root canal treatment was discerned as not feasible for the case. Therefore, the tooth was extracted; a grayish to brownish adherent mass was intimately associated with the roots (Figure 1B). The mass had its epicenter in the furcation area and the mesiodistal aspects of the root trunk.

The lesion was provisionally diagnosed as granulation tissue associated with the tooth and was submitted for histopathological examination. Microscopically, hyperchromatic cells arranged in confluent sheets, nests and fascicles of varying sizes in the connective tissue stroma could be visualized under low power (Figure 2). Discohesive arrangement of cells was noted in some areas.

Under high power, the cells were epithelioid or round to spindle-shaped in morphology. The cells exhibited coarse irregular chromatin with peripheral condensation exhibiting the so-called “peppered moth” nuclei<sup>4</sup> (Figure 3). Presence of brownish granular pigments was noted focally in some cells, suggestive of melanocytic differentiation. Abundant nuclear pleomorphism and anisonucleosis was evident.

A provisional diagnosis of malignant melanoma was decided which was subjective to confirmation by means of immunohistochemistry (IHC), while subsequently ruling out other histopathologically identical lesions. The differential diagnosis included dysplastic nevus, Merkel cell carcinoma (MCC), poorly differentiated squamous cell carcinoma (PDOSCC), Ewing’s sarcoma/ Primary neuroectodermal tumor (EWS/PNET), lymphoma, pigmented cellular schwannoma or carcinoma of neuroendocrine origin.

Diffuse immunoexpression of moderate intensity of Vimentin was noted in the cytoplasm of tumor cells and the stromal elements. Except for focally positive cells, a generalized negative immunoexpression was observed for Cytokeratin AE1/AE3. About 40-50% of the tumor cells exhibited intense immunoexpression of S-100 protein. The tumor cells were immunonegative for Leukocyte common antigen (LCA) and CD99. Intense cytoplasmic immunoexpression of Melan-A and intense membranous immunoexpression of HMB-45 was noted diffusely in the tumor cells.

After the thorough histopathological examination and exclusion of differential diagnosis by means of a panel of biomarkers, a confirmatory diagnosis of malignant melanoma was imparted for the case.

### 3. Discussion

OMM represents less than 0.5% of all oral malignancies, although the incidence has risen rapidly over the last 50 years. While fair-skinned individuals, exposure to sunlight and germline mutation in various genes such as CDKN2A, CDK4, MITF have been considered as risk factors for cutaneous melanoma, the precise etiological factors for OMM are yet to be confirmed.<sup>5</sup> OMM commonly occurs in older individuals, and its risk of occurrence increases with age.<sup>6</sup> The most common age of diagnosis for men is 51 to 60 years and for females in 61 to 70 years. In line with these findings, the present case of OMM occurred in a 63-year-old female.

Melanoma can occur at virtually any cutaneous or mucosal location. While gingiva is considered as a common site of occurrence of OMM, the mode of occurrence in the present case was unusual wherein it occurred within the furcation area of a maxillary molar, without clearly identifiable clinical or radiographic features. A clinician would generally consider it as a granulation tissue, given its clinical presentation in the present case. Suspecting a malignant neoplasm, especially a malignant one such as melanoma would be highly unlikely in such a scenario.

Melanoma exhibits a highly variable histopathological picture which may resemble numerous other entities.<sup>3</sup> Consequently, it has a wide histopathological differential diagnosis, which have to be excluded through careful examination of tissue architecture, cell morphology and assessment of various biomarkers.

Clusters of epithelioid cells with dissociation in focal areas can also be apparent in lesions such as MCC and OSCC. CKs are intermediate filaments specific for epithelial cells, that usually exist in pairs. Melanocytes contain vimentin rather than CK, which is another type of intermediate filament that is generally present in the mesenchymal cells.<sup>7</sup> Absence of CK along with expression of vimentin helps in differentiating melanoma from epithelium-derived carcinomas such as OSCC. Expression CK20 is considered as characteristic for Merkel cells and is essential for diagnosis of MCC.<sup>8</sup> CK AE1/AE3 comprises of both, high-molecular-weight and low-molecular-weight CKs. Negative expression of CK AE1/AE3 also helped in excluding MCC from the differential diagnosis.

A similar histopathological picture of hyperchromatic round cells in clusters or sheets of cells that are negative for CKs and express vimentin can also be noted in EWS/PNET and NHL. Therefore, confirming or excluding these entities is essential for reaching a final diagnosis in such cases. CD99 is a potent marker for tumors deriving from cells of mesenchymal origin such as EWS/PNET, synovial sarcoma, mesenchymal chondrosarcoma, rhabdomyosarcoma.<sup>9</sup> CD45 or LCA is a ubiquitous marker for nucleated hematopoietic cells associated with the immune system. Negative



immunoexpression of LCA and CD99 further excluded lymphoma and EWS/PNET respectively.

S-100 has been traditionally considered as the most sensitive marker for melanoma. In case of carcinomas of neuroectodermal origin or cellular schwannomas, a more diffuse and intense expression of S-100 protein would be present than noted in the present case. However, S-100 is not very specific and can be expressed in cells of other sarcomas such as rhabdomyosarcomas, leiomyosarcoma, peripheral nerve sheath tumors and Langerhans cell histiocytosis.<sup>2</sup> Melan-A and HMB-45 are highly specific and are considered as confirmatory markers for melanoma.

Melan-A is a protein present in the cytoplasm and endoplasmic reticulum of stage I melanocytes involved in the process of melanogenesis. HMB-45 recognizes PMEL17 or gp100 protein present on the membrane of stage II melanosomes.<sup>10</sup> Positive expression of Melan-A and HMB-45 is highly specific for melanocytic differentiation.

Melanoma needs to be distinguished from dysplastic nevus, which can be challenging in certain cases. Dysplastic nevus usually does not exhibit confluence of nests of neoplastic cells as noted in the present case. It is usually restricted to a thickness of less than or equal to three rete ridges. Additionally, it would have only focal positivity for melanocytic markers such as Melan-A and HMB-45, unlike the diffuse expression noted in melanoma.

Although the term ‘melanoma’ suggests a benign neoplasm, it is actually a highly aggressive malignancy with a survival rate of only 27.3% in case of metastases to distant sites. Therefore, the term ‘Melanotic sarcoma’ was rightly described by Lucke in 1869.<sup>11</sup> Even so, the former term has been used universally throughout the years. Early identification of melanoma and prompt radical resection, followed by adjuvant radiotherapy or chemotherapy (in case of metastases), is considered as the optimal treatment strategy for melanoma.

#### 4. Conclusion

Even a lesion that appears to be a mere periapical or periodontal pathology may turn out to be a highly aggressive malignant neoplasm. Therefore, histopathological examination of all the oral lesions is highly recommended, including those occurring in the periapical region. Our case report also emphasizes the role of meticulous histopathological examination and careful planning for assessment of biomarkers in confirmation of diagnosis of melanoma while excluding histopathologically similar entities.

#### 5. Source of Funding

None

#### 6. Conflicts of Interest

None


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**Cite this article:** Mehra SK, Chettiankandy TJ, Sachdev SS, Sardar MA. An unusual presentation of oral malignant melanoma: Disguising as a periapical granuloma. *IP J Diagn Pathol Oncol* 2022;7(2):126–129.