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## **CASE REPORT**

# **Primary Amelanotic Melanoma of the Maxillary Gingiva: A Case Report**

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## **ABSTRACT**

Malignant melanoma arising in the oral cavity is particularly rare. The clinical presentations of malignant melanoma can range from a benign-looking pigmented macule or nodule to a non-pigmented neoplasm which can be categorized into primary or metastatic lesions. Less than 2% of all melanomas show no pigmentation and could lead to misdiagnosis. **Objective:** To present a benign looking but life-threatening malignancy of melanotic melanoma. **Case report:** A 59-year-old female patient was referred to a regional hospital for further treatment of a localized gingival swelling with no ulceration at the anterior maxilla. An incisional biopsy was performed, with initial histopathologic result of a peripheral giant cell granuloma. CT images demonstrated a locally invasive bone destruction compromising the buccal cortical plate. The second biopsy revealed a non-demarcated mass consisting of spindle-shaped to ovoid cells of variable sizes, shapes and staining characteristics, forming short fascicles of various directions in hyalinized and myxoid stroma with focal areas of necrosis, bone invasion and infiltration of vascular wall. The tumor cells strongly expressed Vimentin, S-100, HMB-45 and Melan-A and the diagnosis of amelanotic melanoma was finally made. **Conclusion:** Oral amelanotic melanoma is extremely rare and difficult to diagnose because of the absence of melanin pigment. Immunohistochemistry is a significant tool being used to establish the correct diagnosis.

**Key words:** amelanotic melanoma, malignant melanoma, peripheral giant cell granuloma

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## **INTRODUCTION**

Melanoma is a malignant neoplasm of melanocytes which usually seen on the skin more than the mucosa.<sup>1</sup> Mucosal melanomas are most frequently found in the head and neck region, approximately more than 50% in the oral cavity.<sup>1,2</sup> However, malignant melanoma arising in the oral cavity is particularly rare, accounting for less than 1% of all melanomas<sup>1,3</sup>, and the most frequently affected sites are the hard palate and the gingiva.<sup>2,4</sup> Patients with mucosal melanomas of the oral cavity often are asymptomatic, presenting high incidence in the 5<sup>th</sup> to 8<sup>th</sup> decade of life. Male may be slightly more affected than female.<sup>2,4</sup>

The clinical presentations of malignant melanoma can range from a benign-looking pigmented macule or nodule to a non-pigmented neoplasm which can be catego-

rized into primary or metastatic lesions. The clinical appearance of the tumor is variable and may be classified into the following 5 types: I-pigmented nodular type, II-non-pigmented nodular type, III-pigmented macular type, IV-pigmented mixed type, and V- non-pigmented mixed type.<sup>2,5,6</sup> Less than 2% of all melanomas show no pigmentation. However, up to 75% of oral melanoma are amelanotic.<sup>2</sup> Primary amelanotic or non-pigmented melanoma is a variant of mucosal melanoma which is more difficult to diagnose than that of pigmented lesions because of its benign-looking.<sup>3</sup>

As generally known, the prognosis of mucosal melanoma is poor due to its vertical growth pattern. An overall 5-year survival rate is approximate 15%.<sup>2,7</sup> Furthermore, the prognosis of amelanotic melanoma is poorer than the pigmented type because it tends to locally invade the surrounding tissue and metastasize.<sup>5</sup>

## CASE REPORT

A 59-year-old female patient was referred from a rural hospital for further treatment of a localized gingival swelling without pain or paresthesia at the anterior maxilla for 6 months. Teeth 11 and 21 were mobile and finally extracted. An incisional biopsy was performed on this lesion and the histopathologic examination was initially reported as a peripheral giant cell granuloma. One month later, she noticed that the lesion was getting bigger, and bleeding occurred when chewing or biting food. The patient was then referred to referral Saraburi Regional Hospital for further investigation and excisional biopsy. Gross specimen was sent to Oral Pathology Laboratory, Faculty of Dentistry, Khon Kaen University for further histopathologic investigation and diagnosis.

### Clinical presentation

Extraoral examination demonstrated a mild swelling at the base of nose shallowing bilateral nasolabial folds. Intraoral examination demonstrated a gingival swelling at anterior maxilla from buccal gingiva to vestibular area of 13-23. The lesion is slightly red, having smooth surface and no ulceration. Teeth 11 and 21 were extracted due to severe tooth mobility, and there were some residual blood spots observed on the soft palate as a result of hard food chewing (Figure 1).

### Radiographic examination

OPG demonstrated locally bone destruction in the periradicular area of 15-24 to the hard palate. CT images demonstrated a locally invasive bone destruction compromising the buccal cortical plate (Figure 2).

### Histopathologic examination

The second biopsy was then performed at the referral center and revealed a piece of soft tissue lined by parakeratinized stratified squamous epithelium. The underlying connective tissue demonstrated a non-demarcated mass consisting of spindle-shaped to ovoid cells forming short fascicles of various directions in hyalinized and myxoid stroma. These tumour cells showed ovoid to round nuclei with small nucleoli and amphophilic to eosinophilic cytoplasm. They were variable in size, shape and staining characteristics. Hyperchromatism and frequent mitoses are noted. Focal areas of necrosis, bone invasion and infiltration of vascular wall were also observed (Figure 3).

### Histopathological differential diagnosis

The histopathological examination revealed sheets of spindle-shaped to ovoid cells, large and hyperchromatic nuclei with numerous mitotic figures. These histological features were consistent with a spindle cell malignancy. The histopathological differential diagnosis for this case included several mesenchymal tumours such as neural tumours, vascular tumours, fibroblastic and myofibroblastic tumours, muscular tumours, and some epithelial tumours.



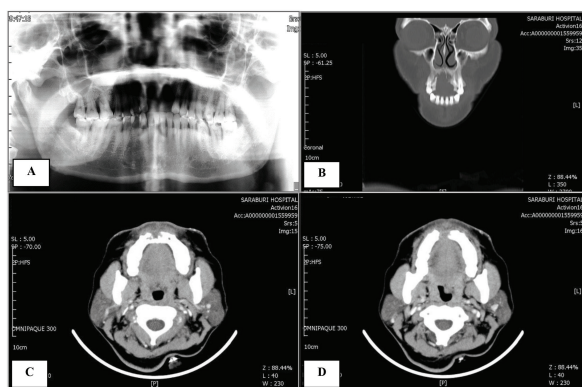
**Figure 1.** (A,B) Extraoral examination demonstrated a mild swelling at the base of nose (arrows); (C) Intraoral examination demonstrated a swelling with no ulceration at buccal vestibule area of 13-23 (outline), and residual blood spots at the posterior soft palate as a result of hard food chewing was observed (arrow).

A panel of immunohistochemical stainings was established by using the following diagram (Figure 4).<sup>8</sup> The first panel of immunohistochemical staining demonstrated that these tumor cell strongly expressed Vimentin and S-100 whereas AE1/AE3, CD34, CD99, SMA showed either negative or weak staining. The second panel of immunohistochemical staining demonstrated that all neoplastic cells were strongly positive for S-100. The ovoid cells were also positive for HMB-45 and Melan A. Other stains including AE1/AE3 and EMA were negative.

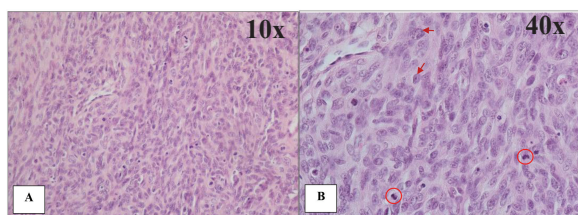
In conclusion, the panels of immunohistochemical staining showed that these tumor cells strongly expressed Vimentin, S-100, HMB-45 and Melan-A. The diagnosis of amelanotic melanoma was finally made (Figure 5).

### Management

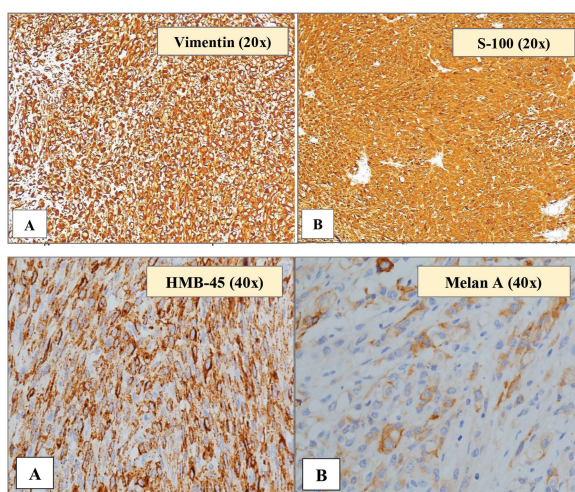
In the present case, there was no primary occult tumour at other sites. The tumour was originated in the oral cavity. Two months after the pathological diagnosis was reported, the patient was referred to the Oral and Maxillofacial Surgery Division for surgical resection (including a partial maxillectomy and bilateral selective neck dissection level I-IV), and reconstruction with obturator under GA. The histopathologic result of cervical lymph node revealed that one metastatic node was detected.



**Figure 2.** (A) OPG demonstrated locally well-defined margin radiolucency with no sclerotic border surrounding the periapical area of 15-24 and involving the hard palate; (B) CT coronal view demonstrated periradicular and palatal bone destruction; (C,D) CT axial view demonstrated a soft tissue mass arising in the anterior maxilla destroying buccal bone through palatal bone.



**Figure 3.** (A) Sections showed numerous spindle-shaped to ovoid cells forming short fascicles of various directions in hyalinized and myxoid stroma; (B) The tumour cells demonstrated ovoid to round nuclei in various sizes with small nucleoli. Hyperchromatism and mitoses are observed (circles)(B).



**Figure 5.** The tumour cells showed positive immunohistochemical staining for HMB-45 (A) and Melan-A (B).

## DISCUSSION

Amelanotic melanoma is a subtype of melanomas which does not produce melanin pigment. It can be primary, recurrent, or metastatic. Primary oral amelanotic

melanoma is a relatively rare malignant tumour which can be found in oral cavity comprising 2% to 8% of all malignant melanomas. The hard palate and the gingiva are the most common sites.<sup>3</sup> The etiologic factors of disease are still not well known.<sup>9</sup> The incidence of the disease is commonly high in the patient older than 40-year.<sup>2,10</sup>

Pigmented mucosal melanoma can be diagnosed clinically following visual signs of melanoma (A-B-C-D-E): A-Asymmetry, B-Border irregularity, C- Color variation, D-Diameter (> 6mm) or Dark, and E-Evolving in size, shape, color or elevation of the lesion. However, the diagnosis of amelanotic melanoma is more difficult than those of pigmented types, and challenges the pathologists due to lack of pigmentation. The surface of the lesion may be smooth which can mislead the clinician to diagnose it as a benign tumour such as pyogenic granuloma.

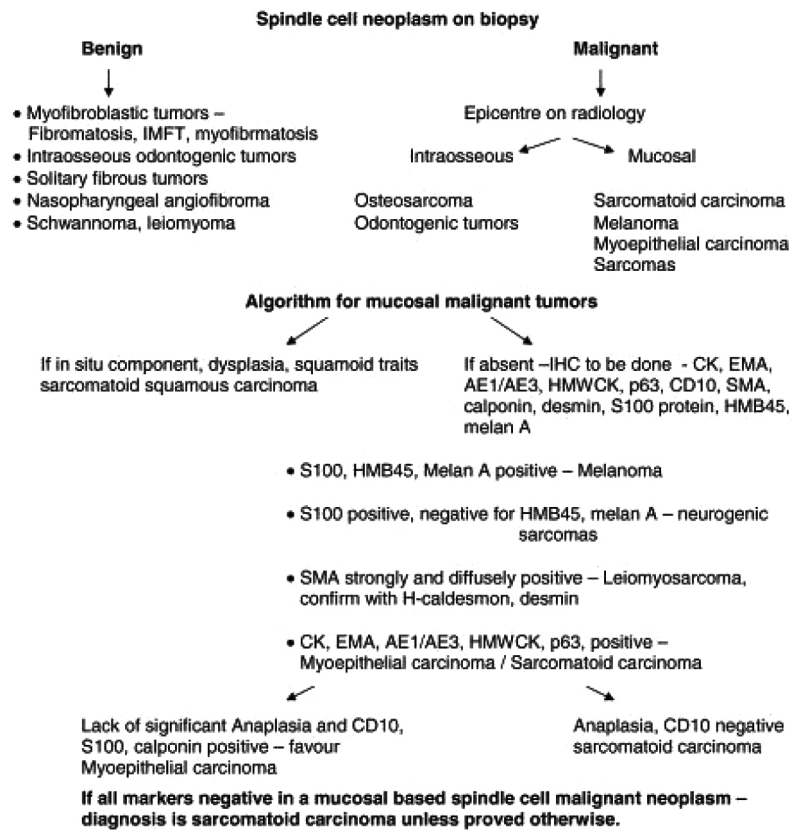
The histopathological examination of amelanotic melanoma reveals a several of spindle-shaped to ovoid cell with large nuclei, mitotic figures and hyperchromatism. No melanin pigment is observed in cytoplasm.<sup>2,3</sup>

Histological differential diagnoses include spindle cell malignancies of mesenchymal tissue, lymphoma, amelanotic melanoma, and undifferentiated carcinoma.<sup>3</sup> Then, the immunohistochemistry is useful for establishing the correct diagnosis.

Anti-S-100, anti-HMB-45 and anti-Melan-A are the most commonly used antibodies for the immunohistochemical diagnosis of primary oral melanoma.<sup>1,2,4,6</sup> S-100 protein is an acidic, calcium-binding protein that is first extracted from bovine brain by Moore in 1965.<sup>11</sup> It is a very sensitive marker to nevus and melanoma cells, and can be used only a screening marker for melanomas because of low specificity.<sup>4,11</sup> S-100 protein has been shown to be present in a wide range of tumors, such as peripheral nerve sheath and cartilaginous tumors, chordomas, Langerhans cell, and carcinomas from various sites including the salivary gland, lung, breast, stomach, colon, endometrium, kidney, and ovary.<sup>11</sup>

Anti-HMB-45, which was first described by Gown et al.<sup>12</sup> in 1986, is an antibody that recognizes the melanosomal glycoprotein gp100.<sup>11</sup> Anti-HMB-45 is regarded more specific but less sensitive than S-100 protein. It is very helpful in distinguishing the differentiated melanomas from other non-melanocytic malignancies.<sup>4,11</sup>

Melan-A is another melanocytic differentiation marker that is identified on melanomas as an antigenic target of cytotoxic T lymphocytes.<sup>11</sup> Prasad et.al studied about melanocytic differentiation markers in malignant melanoma, and reported all of melanoma cases positive to Melan-A.<sup>13</sup> In addition, most studies revealed that Melan-A was higher sensitive and specific to melanomas than S-100 and HMB-45.<sup>6</sup>



**Figure 4.** The diagram demonstrated the diagnostic workflow of spindle cell neoplasms from mucosal based sites in the head and neck

Vimentin, also known as fibroblast intermediate filament, is the major intermediate filament found in non-muscle cells. These cell types include fibroblast, endothelial cells, macrophages, lymphocytes, Schwann cells, and melanocytes. Mesenchymal and endothelial cells usually stain vimentin positive and thus act as a measure of internal quality control in immunoreactivity.<sup>14</sup> In the present case, immunohistochemical staining with antibodies against the S-100, Vimentin, HMB-45, and Melan-A proteins successfully diagnosed this amelanotic case.

The prognosis of oral melanoma is relatively poor but its amelanotic variant has even worse prognosis because it exhibits a more aggressive biology and because of difficulty in diagnosis which leads to delayed treatment.<sup>2,15</sup>

In the present case, the period of time since the patient first noticed the lesion until the day of surgery was almost 1 year because the clinical presentations of the lesion were benign-looking until the patient noticed that the lesion was getting bigger and her teeth became mobile. The histopathologic examination, H&E revealed that the lesion was a malignancy, but the definitive diagnosis could not be confirmed. Therefore, the immunohistochemistry was performed. S-100 and

Vimentin were used for screening the origin of the tumour cell. After that, HMB-45 and Melan-A were used to confirm the diagnosis. Unfortunately, the patient in this case report died six months after surgery.

## CONCLUSION

In summary, oral amelanotic melanoma is extremely rare and difficult to diagnose because of the absence of melanin pigment. Immunohistochemistry is a significant tool being used to establish the correct diagnosis. However, early detection is the most important thing which can lead the patient have the treatment earlier and better outcome.

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