

Malignant Melanoma In The Oral Cavity: A Rare Case Report With Review of Literature

Rajesh Twyana¹, Zhang Hong yi²

¹Yangzte University, Jingzhou, Hubei

²People's First Hospital of Jingzhou Affiliated with Yangtze University, Jingzhou

ABSTRACT

Malignant melanoma is extremely rare neoplasm arising from uncontrolled growth of melanocytes, accounting for 0.5% of all oral malignancies. It has a great tendency to metastasize and locally invade tissues more readily than any other malignant tumor of the oral cavity. It occurs approximately four times more frequently in the oral mucosa of the upper jaw usually on the palate or alveolar gingiva. It present as the rare oral malignant condition, asymptomatic and poor prognosis. The necessity of a highly specialized treatment is factors that should be seriously considered by the involved health care provider. Herein, we report a rare and interesting case of oral malignant melanoma of the maxillary anterior gingiva, which was clinically and histo-pathologically diagnosed with a brief review of literature, has been discussed.

Keywords: gingiva, melanocytes, metastasis, oral melanoma, recurrence

INTRODUCTION

Melanoma is a malignant neoplasm of melanocytic origin that arises from a benign melanocytic lesion. Oral malignant melanoma (OMM) was first described by Weber in 1859.¹ Malignant melanoma of the oral cavity is an extremely rare tumor arising from the uncontrolled growth of melanocytes found in the basal layer of the oral mucous membranes.^{1,2} The World Health Organization (WHO) has defined mucosal malignant melanoma as a malignant neoplasm of melanocytes or of melanocyte precursors. It is characterized by the proliferation of atypical melanocytes at the epithelial-connective tissue interface, associated with upward migration into the epithelium and by invasion of the underlying connective tissues. Melanocytes are neural crest-derived cells that migrate to the

skin, mucous membranes and several other sites. The incidence of melanoma has been steadily increasing in the past several decades with an annual increase of 3-8% worldwide.³ Most common form of melanoma are the cutaneous and the ocular form. Mucosal melanoma involving the sino-nasal cavity, oral cavity, pharynx, larynx, and upper esophagus⁴ rare extremely are and accounts for only 0.5% of all oral neoplasms.⁵ Nearly 80% of oral melanomas arise in the mucosa of the upper jaw, with the majority occurring on keratinizing mucosa of the palate and alveolar gingivae.² It occurs slightly more often in males 2.8:1 (male to female ratio) and the age range is from 20-83 years' worth an average age of 56 years.⁶ The clinical presentation of this condition may vary widely which is divided into following five

Correspondence: *Dr. Rajesh Twyana ; e-mail: rajeshtwyana@yahoo.com*

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types: Pigmented nodular type, pigmented macular type, pigmented mixed type, non-pigmented nodular type and non-pigmented mixed type.^{2,4,6} Non pigments forms of malignant melanoma often cannot be distinguished clinically from other benign or malignant oral tumors which can be diagnosed through biopsy. A pigmented lesion of the oral cavity should be viewed with suspicion since it does not possess clinical specificity.⁷

This case reports of OMM of the maxillary anterior gingiva with cervical lymph node metastasis, which has been discussed with detailed investigations such as biochemical; histopathology, ultrasound and contrast enhanced computed tomography (CECT) to emphasize the necessity for early diagnosis and treatment of this lesion.

CASE REPORT

A 59-year-old male reported to the Out Patient Department, People's first hospital of jingzhou affiliated with Yangtze University, jingzhou, china with a complaint of bluish black discoloration in the upper right gums in relation to the front teeth since 3 months, which started as a pin point lesion, progressed gradually. He gave no history of any systemic illness or trauma to the head and neck region .General physical examination was insignificant and his vital signs were under limits.

Extraoral examination revealed the right submandibular lymph node was palpable and approximately 2 × 2 cm, non-tender, firm, which was fixed to the underlying tissues. On intraoral examination, a diffuse, sessile and asymptomatic swelling, with a smooth surface and of bluish black colour was observed on the maxillary attached gingiva with in relation to right upper central incisor to canine about 3x3 cm in size which was elevated and well-defined. [Figures1]. Based on clinical appearance, pigmented lesions were like melanoacanthoma, nevus and melanoma were considered under differential diagnosis made. Blood investigations and radiographic features did not reveal any significant findings. Incisional

biopsy of the lesion was performed and sent for histopathological examination.

Haematoxylin and eosin-stained sections showed invasion of the connective tissue stroma by sheets and islands of pleomorphic epithelioid, spindle cell atypical melanocytes containing brownish to black pigment in the cytoplasm. The lesion was diagnosed as melanoma. Further this was confirmed immunohistochemically by using Melanin-A, HMB-45, S-100, PCK, LCA and Ki67 which showed strong positivity of the tumour cells [Figure 5].Immunohistochemical report shows Melanin-A(+),HMB-45(+),S-100(+),PCK(-), LCA(-),Ki67(+).

Correlating the patient's complaint, with the history and clinical examination a differential diagnosis of melanosis, amalgam tattoo, drug induced pigmentation, mucosal nevus, melanotic-macule, melano acanthoma and malignant melanoma was arrived. Melanosis is a common benign condition in the oral cavity, Amalgam restorations are not evident, there is no history of any recent medications, mucosal nevi are <0.5 cm in size, melanotic macule are less than 1 cm and are well-circumscribed lesion, melano acanthoma is also a benign tumor, but it can spread up to centimeters in few weeks, Malignant melanoma is a rare aggressive neoplasm, which represents 1-2% of oral malignancies.

A complete blood cell count, biochemical analysis, and urine analysis were insignificant and under normal limits. CECT revealed a well-defined in-homogenously enhancing hypodense nodule in the right maxillary region with no bony erosion and also evidence of a large necrotic right cervical lymphadenopathy.

The radiographic differential diagnosis that were considered are metastatic tumor, tuberculosis and lymphoma were included.

An incisional biopsy was performed the histopathological section shows parakeratinized stratified squamous epithelium with underlying connective tissue stroma. Connective tissue shows atypical melanocytes and melanin

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pigmentation throughout the stroma. Dysplastic features like cellular atypism and anisocytosis are seen in connective tissue stroma suggestive of malignant melanoma [Figure 7]. Work for distant metastases (CT scan of chest, brain and abdomen) was negative.

Based on the clinical examination, radiologic and histopathologic features a final diagnosis of malignant melanoma was arrived. Medical information was provided to the patient and his family regarding the diagnosis, staging, therapeutic options and prognosis.

With diagnosis of primary malignant melanoma of gingiva, surgical intervention was performed with the gingival lesion along the right maxillary alveolar process including teeth was resected. Reconstruction of the defect was done with buccal fat pad flap. The postoperative recovery was found to be uneventful. Histopathology confirmed malignant melanoma with 2 mm tumor thickness with level I lymphnode involvement. The patient was under follow up without no recurrence.



Figure 1: Intraoral photograph showing blackish brown lesion in relation to labial gingiva.



Fig 2

Figure 2: The hematoxylin and eosin–stained section shows melanoma with invasive pattern showing large cells with pleomorphic vesicular nucleus and brown pigment (×40)

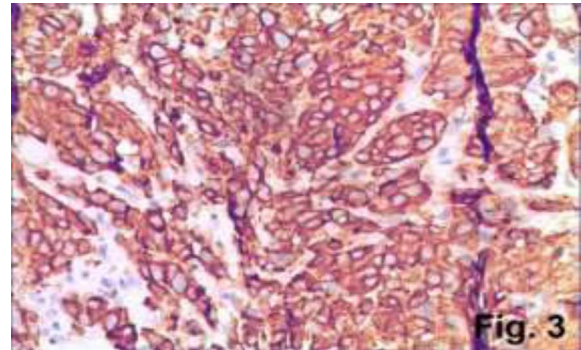


Fig. 3

Figure 3: Immunohistochemical staining with HMB-45 antibody that stains the cytoplasm of the epithelioid cells

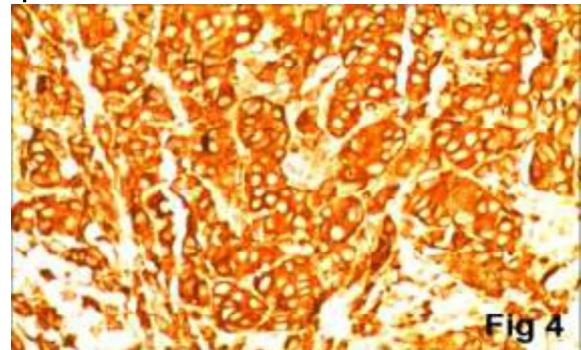


Fig 4

Figure 4: Immunohistochemical staining with Melan-A antibody showing cytoplasmic staining.

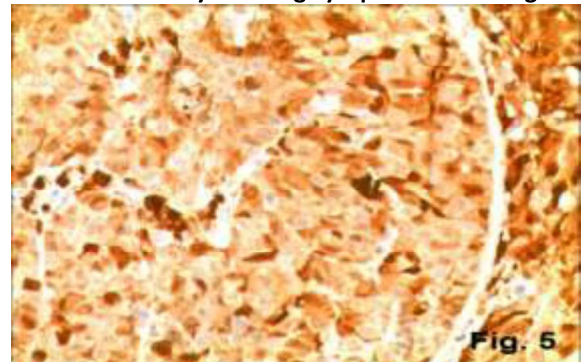


Fig. 5

Figure 5: Immunohistochemical staining with S-100.

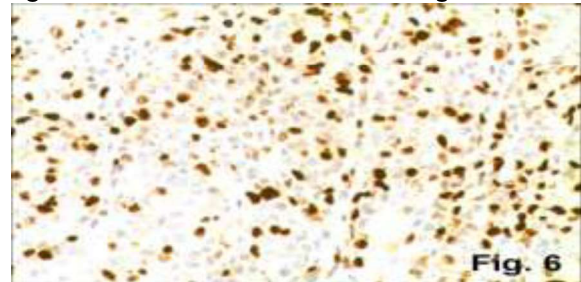


Fig. 6

Figure 6: Immunohistochemical staining with Ki67.

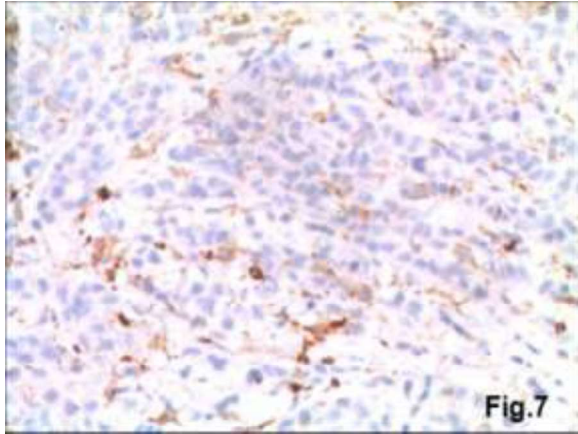


Figure 7: Immunohistochemical staining with LCA.

DISCUSSION

Mucosal melanoma of the oral cavity is a rare malignancy. It has no known predisposing factors and is difficult to diagnose and manage. Differentiating it from a metastatic melanoma is often challenging. Oral malignant melanoma is an extremely rare neoplasm of melanocytes which was reported by Weber in 1856.⁸ It is biologically an aggressive neoplasm with a poorer prognosis than its cutaneous counterpart.

The aetiology of malignant melanoma remains elusive. The risk factors for the development of melanoma include UV radiation, skin and hair colour, numerous freckles, tendency to burn and tan poorly, PUVA therapy, tanning salons, presence of nevi (numerous, large, atypical), xeroderma pigmentosum, immunosuppression, denture irritation, exposure to tobacco, chemicals, petroleum and printing products. Primary oral melanomas originated either from a nevus or pre-existing pigmented lesion currently most thought to arise de novo.^{9,10,11} In our case, patient was not exposed to above factors the possible aetiology may be de novo.

The genetic factors include mutations of the gene CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A), encoding the tumour suppressor protein p16 located on chromosome 9p21 which confers susceptibility to familial malignant melanoma. Other genes include RB1,

CDK4 gene on chromosome 12q15, RB1 and PTEN/MMAC1.^{10,12,13}

Melanomas occur in all ages between 7 and 90 years and are most prevalent in the 5th decade. Males are more commonly affected than females. The most common sites in the head and neck region includes conjunctiva, sinonasal cavity, oral cavity, pharynx, larynx and upper oesophagus (in decreasing order). In the oral cavity 80% cases involves the gingiva and palate.⁹ Occurrence in the mandible, buccal mucosa, lips tongue and floor of mouth is not uncommon.^{11,14,15,16,17} In our case patient presented lesion in the 5th decade of life, which were in the anterior maxillary gingiva. The findings were very similar to the published article in the different journals. That supports the diagnosis as malignant melanoma.

Melanomas are asymptomatic in their clinical appearance and silently progresses and therefore go unnoticed by the patient contributing delay in diagnosis. Early lesions exhibits pigmented patches with alteration in colour and texture of the skin or mucosa. Later lesions shows thick elevated bluish black surfaces with are without ulceration. They are classified (Tanaka et al.) into five types pigmented nodular, non-pigmented nodular, pigmented macular, pigmented mixed, and finally non-pigmented mixed. Some of the tumours are amelanotic. Amelanotic melanoma is a rare tumour which is difficult to diagnose and comprises 10% of all melanomas.^{10, 14,15,16, 18,19} In our case it was pigmented nodular and asymptomatic.

Oral melanoma may not have the typical ABCDE characteristics of skin melanoma but it offers some help in the diagnosis. In our patient all of the ABCDE criteria were present.⁹ Radiographically, primary melanomas rarely involves the jaw bones. If it is involved it should be distinguished from the osteomyelitis.¹⁴

The differential diagnosis of OMM include of oral melanotic macule, melanoplakia, pituitary-based Cushings syndrome, post-inflammatory pigmentation, melanoacanthoma, amalgam tattoo, Addisons disease, Peutz-Jeghers syndrome and melanocytic nevi.^{14,18, 19} But our

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patient did not have any other signs or symptoms suggesting any of these lesions.

Microscopically mucosal melanomas can show two principal patterns: An *in situ* pattern in which the neoplasm is limited to the epithelium and the epithelial-connective tissue interface (junctional), and an invasive pattern in which the neoplasm is found within the supporting connective tissue. A combined pattern of invasive melanoma with *in situ* component is typical for most advanced lesions.^{18,20,21}

The melanocytes present in invasive melanomas show a variety of cell types including epithelioid, spindle and plasmacytoid. They typically have large, vesicular nuclei with prominent nucleoli; mitoses may be present but usually not in large numbers. They are usually aggregated into sheets or alveolar groups and less commonly neurotropic or desmoplastic configurations. In our case the histopathological features coincide with the invasive pattern.

Melanoma shows wide spectrum of histopathological features which are confused with mesenchymal, epithelial and neural tumours, S-100 and HMB-45 are more frequently expressed than Melan-A and these markers are helpful to confirm the diagnosis.²¹ Our case showed positive for HMB-45, Melanin-A,S-100,Ki67.

Greene *et al.*²² proposed the criteria for primary malignant melanoma which includes: (1) Demonstration of melanoma in oral mucosa (2) Presence of junctional activity (3) Inability to demonstrate extra oral primary melanoma. Our present case fulfills the above criteria.

The Clarks grading system assessing the depth of invasion and Breslow measuring the thickness of tumour from the surface of the epidermis to the greatest depth of the tumour have no validation as prognostic factors in OMM due to rarity of the lesion and absence of a true dermis in the oral cavity. However, a simple TNM staging with prognostic value have three stages.^{11,14, 16,19,21,23} The present case fits into Level 2 Stage 1.

The common sites of metastases are lymph nodes, liver and lungs, with wide dissemination in the advanced disease. The treatment policy

for OMM is unclear but an excisional biopsy of the lesion followed by a wide surgical excision where the diagnosis is proven is current choice for most of the surgeons with radiotherapy and chemotherapy as adjunctive treatment methods. But in our case, there was only metastasis to the lymph node only.

It has always been suggested that cutting into malignant neoplasm during incisional biopsy could result in accidental dissemination of malignant cells within adjacent tissues or blood or lymphatic stream with subsequent risk of local recurrence or regional or distant metastasis. Rampen *et al.* and Austin *et al.* did find a somewhat reduced survival rate in patients with melanoma who had incisional biopsies but against the studies done by Lederman and Sober where they found no correlation in patient's prognosis with incisional and excisional biopsies. Recurrences may occur even after 10–15 years after primary therapy. Distant metastasis to the lungs, brain, liver, and bones are frequently observed.²⁴

It is well known that early diagnosis and treatment of melanoma can reduce mortality. If diagnosed early when the malignant cells are limited to the epithelium or invasion is minimal. Melanoma is either 100% curable by excision (for *in situ* lesion) or is associated with a 5-year survival rate of 95% (for lesions <1 mm in thickness and without ulceration). In contrast, the 5-year survival rate for cutaneous melanomas >4-mm thickness with ulceration is only 45%.^{20,25}

Poor prognosis of melanoma may be due to early invasion of deeper structures due to proximity of bone and muscles increasing likelihood of metastasis. Rich vascular supply of oral cavity further aids in dissemination of melanoma.²⁶ A variety of serological markers like serum lactate dehydrogenase (LDH), melanoma-inhibiting activity (MIA), S100B and vascular endothelial growth factor (VEGF) are available for melanoma. Elevated levels of LDH and MIA are associated with more advance stages and poorer prognosis. These markers are useful in monitoring the patient's clinical course of the disease and response to therapy.⁸

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The reported average duration of life from the point of diagnosis was about 18 months and 79% of patients died within 5 years. Few authors reported that the 5-year survival rate of intraoral melanoma does not exceed 5-9%. In general, the survival rates are poor and are worst for those cases with metastasis.^{19, 27}

The treatment options for mucosal melanomas of oral cavity include surgery, radiation and adjuvant chemotherapy and/or immunotherapy. Surgery is the mainstay of treatment, but it may be challenging, depending on the anatomic location within the oral cavity and extent of the tumor. Optional treatment of clinically negative neck nodes with neck dissection or radiotherapy was recommended because of the high risk of subclinical disease.²⁸ Although melanoma is classically not radiosensitive, some authors have described improved survival and local control with postoperative radiotherapy.²⁹

CONCLUSION

Despite the improvement of surgical techniques and the introduction of new chemotherapeutic agents, prognosis of this malignancy remains poor. OMMs are rare, but aggressive tumors with very low survival rates which can metastasize rapidly. Towing to its rarity, all pigmented lesions in the oral cavity should be examined with suspicion. The treatment of choice for oral melanomas is wide surgical resection with or without neck dissection depending upon chemotherapy as an adjuvant or palliative therapy. However, close patient monitoring is imperative to check for recurrence. Hence, the purpose of this manuscript is to emphasize on early diagnosis and to maintain high index of suspicion for those pigmented lesions occurring in the high risk sites such as palate and maxillary gingiva. In our case, early diagnosis helped to perform early surgery with no recurrence was found eight month postoperative.

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