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Research Paper

Pigmented Malignant Lesion: Report of a Case With Review of Literature

Medical Science

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ABSTRACT

The colour of the oral mucosa is usually determined by the degree of keratinization, melanin activity and the vascularity in the underlying mucosa. Any change in the colour is due to the variations in these factors, of which melanin activity will lead to brown to blackish coloration. Since the change in the melanin activity can be a physiological adaptation or a true pathologic growth, pigmented lesions should be seen with certain amount of suspicion. The only true pigmented malignant lesion is the Malignant Melanoma which is a rare tumor in the oral cavity. Here, we present a case of malignant melanoma with review of literature highlighting the diagnostic criterias and recent treatment modalities.

INTRODUCTION:

Melanoma is a malignant tumor of melanocytes which is potentially aggressive and arise in skin mostly. But it may also arise from mucosal surfaces or at other sites wherein neural crest cells migrate.[1] Melanocytes, normally situated in the basal layer of oral epithelium and epidermis, embryologically arise from neural crest ectoderm and enter the epithelium at about 11th week of gestation. They produce melanin which is an endogenous pigment and contribute to the colour of oral mucosa.[2]

The incidence accounts to approximately 1 % of all melanomas. The most frequently affected oral sites are the palate and maxillary gingiva.[3] The peak age of occurrence is between 65–79 years, which is at an average of 1–2 decades later than cutaneous melanoma.[4] It has a male preponderance and is more common in Japan and Africa than in Western countries.[5]

The lack of early signs and symptoms make these lesions easily mistaken for other more common diseases due to which they have a poorer prognosis than their cutaneous counterpart. Because they are diagnosed at advanced stages, their five year survival rate is 15-38%.[6]

Pigmented lesions of the oral cavity should be viewed with suspicion, because it does not possess clinical specificity and therefore must be differentiated from other forms of pigmented oral disease.

CASE REPORT:

A 50 year old male patient presented with a black swelling in the upper front tooth region and palate. The swelling was noticed two months prior and gradually increased in size to attain the present size. There was no history of pain, weight loss or similar growths in the same region or elsewhere in the body. He was a smoker since 25 years, smoking 20 cigarettes per day. On general examination, the patient was moderately built and nourished with all vital signs within physiological limits.

On intraoral examination, a well-defined brownish black exophytic growth with a lobulated surface was seen in the anterior maxillary labial gingiva measuring about 2 x 3 cm (Fig 1). The lesion was seen to extend onto the palate as a discoloured patch with irregular margins (Fig 2). No secondary changes were observed. On palpation, the growth was non tender, soft to firm in consistency, non-fluctuant, non-compressible, non-reducible and non-pulsatile. Regional lymph nodes were non palpable. Provisional diagnosis of malignant melanoma was given and incisional biopsy was performed.

Hematoxylin and Eosin (H & E) stained sections revealed connective tissue stroma composed of sheets of tumors cells containing melanin pigment (Fig 3). The atypical melanocytes were large, round to oval or polygonal in shape with cells showing variations in sizes. Hyperchromatic nuclei with nuclear pleomorphism and numerous mitotic figures were also noted (Fig 4). Based on the histopathologic findings, diagnosis of malignant melanoma was made.

The patient was referred to regional cancer centre for further treatment and was lost for follow up.

DISCUSSION:

Melanoma is a malignant neoplasm of melanocytic origin that arises from a benign melanocytic lesion or de novo from melanocytes within an otherwise normal skin or mucosa.[7] Oral melanoma accounts for 0.5 % of all oral malignancies.[8] Oral melanoma occurs between 30-90 years with high occurrence in 6th decade of life. It does not have gender preference, but some authors report a slight male dominance.[9]

The aetiology is unknown with various etiologic agents like tobacco use, chronic irritation from ill-fitting dentures[8] and ingested and inhaled environmental carcinogens at high internal body temperature being suggested.[10] They mostly arise de novo, from apparently normal mucosa with only 30% being preceded by oral pigmentations which lasts for several months or even years.[5] Recently, p53 protein alteration has been identified with a recent study demonstrating that melanoma progression is due to loss of heterozygosity at 12p13 and loss of p27KIP1 protein expression.[11] To understand the pathogenesis of Oral Malignant Melanoma (OMM), cytogenetic analysis and evaluation of melanocytic- specific gene- 1 (MSG-1) seems to be very helpful.[12] In the present case, the patient was a 50 year old male, with smoking habit for about 25 years.

The initial finding in OMM is a swelling, which is usually pigmented either uniformly brown or black, or may show variations in colour.[13] In amelanotic melanomas, pigmentation is absent.[14] The surface may be smooth and intact or may be ulcerated.[15] Based on the clinical appearance, Tanaka et al identified five types of OMM: Pigmented nodular type, Non pigmented nodular type, Pigmented macular type, Pigmented mixed type and Non

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pigmented mixed type.[14]

Delgado et al proposed a simple clinical diagnostic method ("rubbing a gauze") but the procedure seems questionable.[16] Fine needle aspiration or exfoliative cytology of primary pigmented lesions are contraindicated.[17] The ABCD checklist ("Asymmetry", "Border" irregularities, "Colour" variegation and "Diameter" >6mm) which is commonly used in the identification of cutaneous melanoma, is also of some use in the diagnosis of oral melanoma. When a confident diagnosis cannot be given on clinical basis, a biopsy is mandatory in order to exclude OMM.[18] Radiological examination through computed tomography, magnetic resonance imaging or positron emission tomography (PET) could be useful for evaluation of primary tumour and regional or distant metastases.[17]

An excisional biopsy with a 1 to 2 mm margin for small lesions in amenable locations and incisional biopsy through the thickest or the most suspicious part of the tumor for large lesions is recommended. But there is subsequent risk of local recurrence, or regional or distant metastasis due to accidental dissemination of malignant cells within the adjacent tissues ("seeding") or even in the blood or lymphatic stream.[18]

Greene et al proposed three criteria for the diagnosis of primary OMM: Demonstration of malignant melanoma in the oral mucosa; Presence of so called 'junctional activity' (i.e., Melanocytes arranged along the basal layer of the surface epithelium) in the lesion and inability to show malignant melanoma at any other primary site.[19]

Microscopically, the surface epithelium may be flattened and there may be ulceration; with some OMMs showing pseudoepitheliomatous hyperplasia.[20] Malignant cells show a wide range of shapes, including spindle, plasmocytoid, clear cell and epithelioid ones. OMMs can be histologically subclassified into: In situ melanoma, which is limited to the epithelium and the epithelium – connective tissue interface; Melanomas with an invasive pattern, in which the neoplasm extends into the connective tissue; Melanomas with a combined pattern of invasive melanoma and in situ component.[13] The presence of melanin pigment in the ductal epithelial cells of the underlying salivary glands, using the term "melanogenic metaplasia" has also been reported.[21]

The histological grading system of Clark and Breslow were proposed to detect the level of tumor invasion.[7] OMM can be diagnosed on H&E stained sections with confidence. If pigment is completely absent immunohistochemical stains using markers like S-100, gp100 (HMB – 45), Mart – 1 (Melan- A) are of help.[22]

The 2002 (revised) TNM Melanoma Staging System of the American Joint Committee on Cancer does not have published guidelines for OMM staging but a simple TNM clinical staging system for Head and Neck Malignant Melanoma(HNMM) (including OMM) has shown to be of prognostic value. A recent histopathologial microstaging for Stage 1 subclassifies the three levels (Table 1).[19]

Table 1: Clinical Staging System for OMM with histopathological microstaging for Stage 1[19]

Stage 1	Primary tumour present only (T_{any} N0 M0)
Level 1	Pure in situ melanoma without evidence of invasion or in situ melanoma with "microinvasion"
Level 2	Invasion up to the lamina propria
Level 3	Deep skeletal tissue invasion into skeletal muscle, bone or cartilage
Stage 2	Tumour metastatic to regional lymph nodes (T_{any} N1 M0)
Stage 3	Tumour metastatic to distant sites (T_{any} N_{any} M1)

Treatment of OMM is controversial with several studies indicating radical resection as primary treatment. Umeda and Shimada's protocol suggests the extent of the surgical margins.[23]

Recurrences could develop due to the presence of atypical melanocytes in the surgical margins or presence of satellites. Even though OMMs are regarded as poorly radiosensitive, postoperative radiotherapy is generally recommended if poor prognostic pathologic features are present.[24]

Adjuvant chemotherapy with decarbazine, platinum analogs, nitrosureas and microtubular toxins have been used for palliative purposes and postoperative chemotherapy with dimethyl triazeno imidazole carboxamide (DTIC), nimustine hydrochloride (ACNU) or vincristine (VNC). Anticancer therapy using IFN-ɣ and anti-Fas antibody has also shown good results.[24] Cancer testis antigens (CTAs) expression profile could lead to the development of a new vaccine-based therapy with gene therapy still in an experimental phase.[10]

Prognostic determinants of the disease includes clinical staging, tumor thickness greater than 5mm, presence of vascular invasion, necrosis, polymorphous tumour cell morphology and the inability to properly resect the lesions with negative margins.[3]

Despite the improvement of surgical techniques and the introduction of new chemotherapeutic agents, prognosis of this malignancy remains poor with 5-year survival rate for HNMM ranging from 21% to 40% and for OMM being 15%, with a median survival of 25 months.[3] Recurrences may occur even 10-15 years after primary therapy with distant metastases to the lungs, brain, liver and bones being frequently involved. [25]

Fig 1: Intraoral photograph showing a well-defined brownish black exophytic growth with a lobulated surface in the anterior maxillary labial gingiva

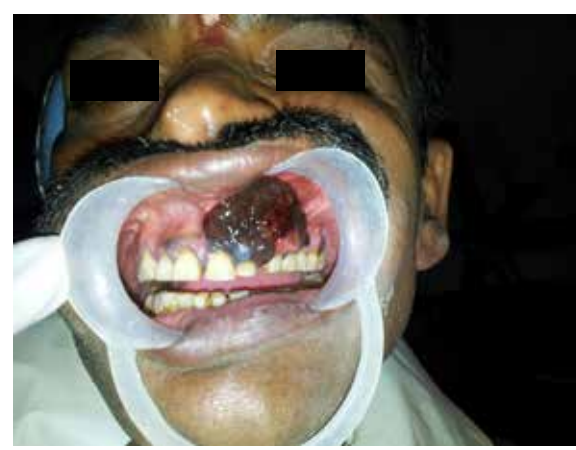


Fig 2: Intraoral photograph showing the extension of discoloured patch with irregular margins on the palate.

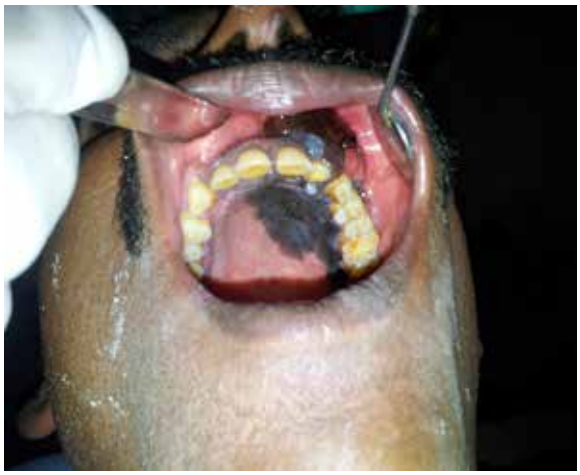


Fig 3: 100X magnification, H & E stained section showing connective tissue stroma with sheets of tumor cells containing melanin pigment.

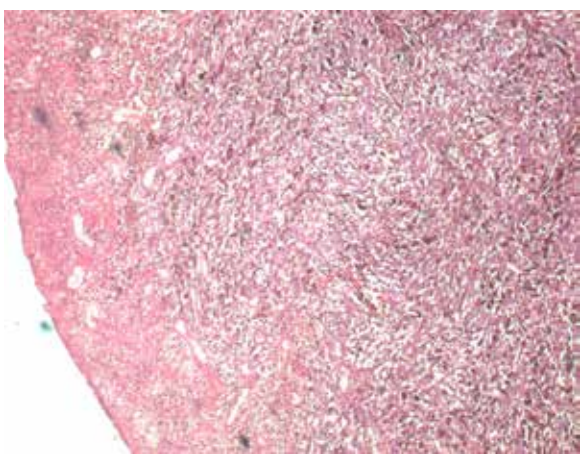
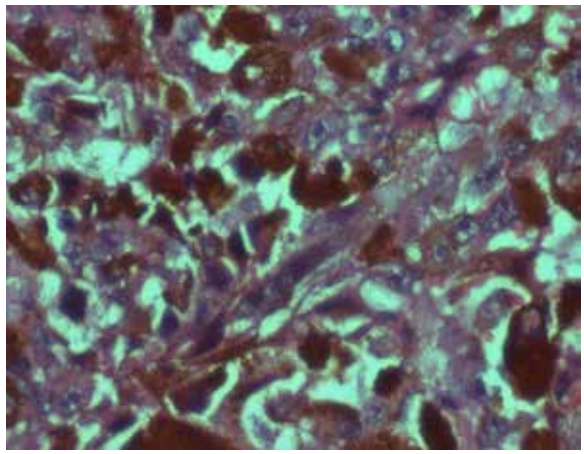


Fig 4: 400X magnification, H & E stained section showing atypical melanocytes



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