ORIGINAL RESEARCH PAPER

Volume-8 | Issue-6 | June-2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ORAL MALIGNANT MELANOMA - A BRIEF REVIEW

Dental

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ABSTRACT

Malignant melanoma is the most common cutaneous cancer after squamous cell carcinoma and basal cell carcinoma of the skin. Oral malignant melanomas are quite rare and are diagnosed at later stages. Oral mucosal melanomas commonly occur on the palate and the maxillary mucosa. The pathogenesis and clinical behavior of oral melanoma is different from that of cutaneous melanoma. The grading and histopathological, immunohistochemical (IHC) markers (S100 & Human melanoma black-45) for diagnosing oral malignant melanoma has been elobrated in this review

KEYWORDS

Oral malignant melanoma, IHC, S100, HMB45, vertical growth phase, radicular growth phase.

DEFINITION:

Melanoma is a malignant neoplasm of melanocytic origin; it may arise *de novo* or from a preexisting benign melanocytic lesion. It is a neoplasm of epidermal melanocytes.

It is one of the more biologically unpredictable and deadly of all human neoplasms. [1]

Although it is the third most common cancer of the skin (basal and squamous cell carcinomas are more prevalent), it accounts for only 3% of all such malignancies.

Cutaneous melanoma is increasing in incidence. Cutaneous malignant melanoma is the most rapidly increasing cancer in whites. [2]

ETIOLOGY:

The following environmental and genetic factors are described in the etiology of malignant melanoma.

1. ENVIRONMENTAL FACTORS

a) *Sun exposure*: The highest incidence of melanoma has been reported from areas with long hours of sunlight throughout most of the year. Lower risk for melanoma was reported in patients who had low amount of UV light. Intermittent exposure to high intensity UV seems to be more detrimental than continual exposure in its causation.[3] Exposure in childhood appears to be particularly important. Recreational activity leading to sunburns in adulthood, such as sailing, has also been incriminated as an etiological factor.[1]

b)Artificial UV sources. Several case-control studies of melanoma risk and tanning lamp use have demonstrated a positive relation, suggesting that longer wave artificial UVA may play a part in the etiology of melanoma in addition to exposure to natural sunlight. [4]

c)Socioeconomic status: Several studies have reported that melanoma is more prevalent in those of high socioeconomic status.

d) Fair skin, freckles, red-hair: These phenotypic characteristics increase the risk of melanoma. [5]

e) Number of melanocytic nevi: The total number of melanocytic nevi, dysplastic or bland, has been reported by several groups as a strong risk factor.

2. GENETIC FACTOR:

***a) Familial melanoma*:** Between 2 and 5% of melanoma patients have a positive family history of melanoma in at least one first- degree relative. [6]

b) *Xeroderma pigmentosum:* In this genetically determined disorder, defective DNA repair mechanisms lead to excessive chronic UV damage and subsequent development of different sun-related skin tumors, including melanoma, in sun-exposed areas.[5]

PATHOGENESIS OF MELANOMA:

For many years, it was believed that many melanomas developed in preexisting pigmented nevi, particularly junctional nevi.

I. However, Clark and his colleagues are of the opinion that junctional nevi are not histogenetically related to melanomas. [7] It is quite possible that lesions which were interpreted as junctional nevi were, in fact, premalignant melanocytic dysplasia of some type, thus leading to the erroneous concept of malignant transformation of nevi.

Melanomas may develop in or near a previously existing precursor lesion or in healthy-appearing skin. [8]

A malignant melanoma developing in healthy skin is said to arise de novo, without evidence of a precursor lesion. Certain lesions are considered to be precursor lesions of melanoma, including the common acquired nevus, dysplastic nevus, congenital nevus, and cellular blue nevus.[9]

Although benign, intraoral melanocytic proliferations (nevi) occur and are potential sources of some oral melanomas; the sequence of events is poorly understood in the oral cavity. Currently, most oral melanomas are thought to arise de novo. [10]

In 1975, Clark and his coworkers presented an interesting concept regarding the developmental biology of cutaneous melanoma. They documented two phases in the growth of melanoma: the *radial-growth phase* and the *vertical-growth phase.[9]*

The radial-growth phase is the initial phase of growth of the tumor. During this period, which may last many years, the neoplastic process is confined to the epidermis. Neoplastic cells are shed with normally maturing epithelial cells and although some neoplastic cells may actually penetrate the basement membrane, they are destroyed by a host-cell immunologic response. [11]

The vertical-growth phase begins when neoplastic cells populate the underlying dermis. This takes place because of increased virulence of the neoplastic cells, a decreased host-cell response, or a combination of both. [12]

Metastasis is possible once the melanoma enters the vertical-growth phase. It is recognized that not all melanomas have both radial- and vertical-growth phases. Nodular melanoma (q.v.) exists only in the vertical-growth phase. [10]

II. Environmental exposure (UV light) + **genetic susceptibility** (*CDKN2A*, *CDK4*, *MC1R*, *BRAF*, *p16/ARF* genes) → **accumulation of genetic mutations** in melanocyte that activate oncogenes, inactivate tumour suppressor genes and impair DNA repair → melanocyte proliferation, blood vessel growth, tumour invasion, evasion of immune response, metastasis. [13]

CLINICAL FEATURES:

AGE: Although the lesion occurs over a broad age range, most cases arise in individuals 45 through 84 years old, with a median age at diagnosis of 61 years.

SEX: There is a female predilection among patients younger than 40 years (possibly related to tanning bed use); in contrast, a male predilection is seen among older patients.

SITE: The most frequent primary site in men is the back, whereas in women the lower extremities are affected most commonly.[14]

- **A**symmetry (because of its uncontrolled growth pattern)
- **B**order irregularity (often with notching)
- **C**olor variegation (which varies from shades of brown to black, white, red, and blue, depending on the amount and depth of melanin pigmentation)
- **D**iameter greater than 6 mm (which is the diameter of a pencil eraser)
- **E**volving (lesions that have changed with respect to size, shape, color, surface, or symptoms over time)

Fig1: The following criteria aid clinical diagnosis of melanoma

Cutaneous melanoma has been classified into a number of types. However, the most common types are: superficial spreading melanoma; nodular melanoma; lentigo maligna melanoma (Hutchinson's freckle); and acral lentiginous melanoma. [15]

CLINICAL SUBTYPES

	Superficial spreading melanoma (70%)	Nodular melanoma (15%)	Lentigo malignant melanoma (10%)	Acral lentiginous melanoma (5%)
Location	• Any site • Lower extremities in women; back in men	• Trunk, head, neck	• Face, neck, arms	• Palmar, plantar, subungual, mucosal
Morphology	• Macule or plaque • Irregular, asymmetric border • Ulceration or bleeding with growth	• Papule or nodule • Irregular border • Ulceration, bleeding	• Macule • Irregular border • Raises with growth	• Macule or patch • Irregular border • Gradual thickening and ulceration with growth
Colour	• Variable: red, blue, black, white	• Dark: black, blue	• Starts tan brown, "stain-like" → turns dark brown, black	• Variable: dark brown, black, blue
Pathophysiology	• Prolonged radial growth of atypical melanocytes confined to epidermis (months to years) • Malignant cells eventually invade dermis with rapid vertical growth	• Early onset invasion into dermis, vertical growth and metastases • Rapid growth (weeks to months) • No radial growth phase *Rapidly fatal	• Begins as a solar lentigo maligna with slow radial growth confined to epidermis (5-20 years) • Malignant cells eventually invade dermis with rapid vertical growth	• Prolonged radial growth of atypical melanocytes confined to epidermis (months to years) • Malignant cells eventually invade dermis with rapid vertical growth *Most common subtype in people with darker skin

Rare variants of melanoma

- **Nevoid melanoma:** tan, dome-shaped nodule, > 1 cm, resembles a benign nevi.
- **Desmoplastic melanoma:** firm, skin-coloured nodule or plaque, resembles a scar.[11]

CLARK AND BRESLOW STAGING:

Clark and Breslow staging and risk[11]

Clark scale (level of invasion)		Breslow scale (vertical thickness)	Risk for metastasis
I	Epidermis (in situ)	in situ	None
II	Invades papillary dermis	<0.75 mm	Minimal (excellent prognosis)
III	Fills the papillary dermis to papillary-reticular junction	0.75–1.5 mm	Significant/medium
IV	Invades reticular dermis	1.51–4.0 mm	High
V	Invades subcutaneous fat/tissue	>4.0 mm	Extremely high

Fig 2: Clark and Breslow staging of melanoma

ORAL MANIFESTATIONS.

Malignant melanoma is an uncommon neoplasm of the oral mucosa. Of epidemiologic interest is the fact that melanoma of the oral mucosa is one of the most common sites for the neoplasm in Japanese. Melanomas in Blacks are seldom found in the skin yet occur on mucous membranes and on the plantar skin.[10] Primary oral melanoma is nearly twice as common in men as in women. Primary oral melanoma is nearly twice as common in men as in women. The overall age of occurrence is approximately 55 years. The oral melanoma exhibits a definite predilection for the palate and maxillary gingiva/alveolar ridge. [8] Cases are also recorded on the buccal mucosa, mandibular gingiva, tongue, lips and floor of the mouth. The lesion usually appears as a deeply pigmented area, at times ulcerated and hemorrhagic, which tends to increase progressively in size .[10]

HISTOPATHOLOGICAL FEATURE:

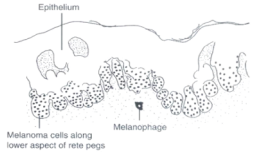

Fig 3: Histopathological diagram of melanoma

- The malignant cells often nest or cluster in groups in an organoid fashion; however, single cells can predominate.
- The melanoma cells have large nuclei, often with prominent nucleoli, and show nuclear pseudo-inclusions due to nuclear membrane irregularity.
- The abundant cytoplasm may be uniformly eosinophilic or optically clear. Occasionally, the cells become spindled or neurotized in areas.
- This finding is interpreted as a more aggressive feature, compared with findings of the round or polygonal cell varieties.
- The intraepithelial component (radial-growth phase) of superficial spreading melanoma is characterized by the presence of large, epithelioid melanocytes distributed in a so-called 'pagetoid' manner.
- This pagetoid spread within the epidermis is sometimes known as 'buckshot scatter'.
- As long as the malignant cells are confined to the epithelium, there is no host- cell response in the underlying connective tissue.
- When melanocytes penetrate basement membrane, a florid host-cell response of lymphocytes develops. Macrophages and melanophages may be present.
- The tumor cells are often destroyed by this cellular response. The vertical-growth phase is characterized by the proliferation of malignant epithelioid melanocytes in the underlying connective tissues.
- The cells may be arranged singly or in clusters. Melanin pigment is usually scanty. [14]

ULTRASECTIONAL FINDINGS:

Premelanosomes and Melanosomes are commonly seen.

IHC STAINS:

- Although immune-histochemical stains are usually not necessary for diagnosis, they are generally performed for confirmation.
- Both S-100 and homatropine methylbromide (HMB45) stains are positive in melanoma.
- The S-100 is highly sensitive, although not specific, for melanoma, while the HMB45 is highly specific and moderately sensitive for melanoma.
- The 2 stains, in concert, can be useful in diagnosing poorly differentiated melanomas.

- Vimentin is positive in most cases.
- Recently, microphthalmic transcription factor, tyrosinase, and melano A immunostains have been used to highlight melanocytes.

S100 - acidic calcium-binding protein that was first discovered in glial cells; its name is because of its solubility in 100% saturated ammonium sulfate solution.

It is a commonly used sensitive marker for melanoma as well as nerve sheath and granular cell tumors and myoepitheliomas.

In melanomas, S100 is present in the nucleus and cytoplasm and has a sensitivity of 97–100%.

However, the specificity of S100 for melanocytic lesions is limited, it being expressed in nerve sheath cells, myoepithelial cells, adipocytes, chondrocytes and Langerhans cells and the tumors derived from these cells.

HMB-45:
HMB45, a marker of the cytoplasmic pre-melanosomal glycoprotein gp100, was one of the first melanoma specific' markers discovered.

It is not as sensitive as S100 but has greater specificity. In positive melanocytic lesions, HMB45 is expressed in the cytoplasm. [16]

CONCLUSION:

As oral malignant melanomas are asymptomatic with rapid growth potential, they are usually diagnosed at the late stage. Early oral diagnosis and biopsy of suspected pigmented and non pigmented lesions are much needed. By diagnosing these lesion early, the patients rate of survival and prognosis can be increased.

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