REVIEW ARTICLE

ORAL MELANOTIC LESIONS: A CLINICIAN’S MAZE

ABSTRACT

The diagnosis of oral melanotic lesions within the oral cavity is often challenging. The clinical appearance of these lesions appear similar hence definitive diagnosis calls for the need of detailed histopathological evaluation. The colour, location, duration, distribution and appearance of melanotic lesions along with past medical history play an important role in arriving at an accurate diagnosis.

Key words: Melanin, Pigmentation, Macule.

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The identification of pigmented tissue within the oral cavity poses a diagnostic dilemma for the clinician. The colour of oral mucosa varies in different physiological and pathological conditions. The clinical presentation of mucosal pigmentation is variable and can range from focal to diffuse macule, small nodular growth to a large mass. They may be black, gray, blue, purple or brown in color. The color of oral pigmentation may vary depending upon the quantity, depth or location of the pigment. Generally, the surface shows brown pigmentation and those located deeper are black or blue.

Melanocytes are located in the stratum basale and produce melanin. Melanin is transferred to adjacent keratinocytes via membrane-bound organelles called melanosomes. When skin is exposed to sunlight, melanocytes produce more pigment, causing the skin to tan. Sometimes clusters of melanocytes form non cancerous (benign) growths called moles. Moles can be either flat or raised, round or oval, and are smaller than a pencil eraser. (Generally harmless, but can become cancerous).

Melanin pigments can be classified into two major types eumelanin (dark brown and black) and pheomelanin (yellow, red, and light brown) based on their biosynthetic pathways. Human melanocytes reside not only in the epidermis and in hair follicles but also in mucosa, cochlea of the ear, iris of the eye, and mesencephalon of the brain as well as other tissues.

**WORKING CLASSIFICATION**

A precise classification of these lesions will guide the clinician for better diagnosis and treatment planning.

**Based on the etiology**

- a. Endogenous factors
- b. Exogenous factors
  
  - a. Endogenous factors
    - 1. Physiologic pigmentation
  
  - b. Exogenous factors
    - 1. Drug induced
    - 2. Heavy metal exposure
    - 3. Smokers melanosis

Oral pigmentation may be exogenous or endogenous in origin. Exogenous pigmentation is mainly associated with foreign-body implantation in the oral mucosa. Endogenous pigments include melanin, haemoglobin, hemosiderin and carotene.

**Description of lesion**

**Physiologic pigmentation (Racial Pigmentation)**

Physiologic pigmentation occurs as a result of increase in the production of melanin pigment by basal melanocytes. The hue of physiologic pigmentation varies from light brown to black in colour. Physiologic pigmentation can be either multifocal or diffuse in nature and is influenced by physical, mechanical and chemical stimulation. (Dummet et al) Ethnic pigmentation is symmetrical in distribution and rarely affects the surface topography or disturbs the normal stippling of gingiva.

It is more evident in darker skinned individuals. It is more common in African, Asian and Mediterranean populations. Physiologic pigmentation occurs as a result of greater melanocyte activity rather than greater number of melanocytes. The most common location are attached gingiva, buccal mucosa, hard palate, lips and tongue.
GENETIC DISORDERS

Peutz-Jeghers syndrome

The Peutz-Jeghers syndrome is characterised by mucocutaneous macules, intestinal hamartomatous polyposis, and increased risk of carcinomas of the gastrointestinal tract (small intestine), stomach, colon pancreas, breast, and thyroid. It has Autosomal dominant mode of inheritance with germline mutations involving the gene STK11/LKB1.

Oral lesion may appear as black-to-brown spots of less than 1 mm in size and are typically localized in the lower lip and perioral area. As age progresses melanotic macules in the oral cavity may eventually fade or disappear and perioral lesions tend to persist.

The clinicopathologic criteria by World health organisation include (Any one criteria is sufficient enough for the diagnosis of Peutz-Jeghers syndrome)

1. Three or more polyps, with histological features of PJS
2. A family history of PJS with any number of polyps
3. A family history of PJS with characteristic mucocutaneous pigmentation
4. Characteristic mucocutaneous pigmentation with any number of polyps.

McCune Albright syndrome

McCune Albright syndrome (MAS) is characterised by polyostotic fibrous dysplasia in combination with extra skeletal manifestations which include endocrinopathy and cafe au lait macules. MAS commence with the appearance of Cafe-au-lait spots which are apparent at or shortly after birth. These lesions are evident along the midline of the body and are characterised by irregular, jagged borders which are said to resemble the ‘Coast of Maine’, in contrast to the smooth-bordered ‘Coast of California’ macules seen in Neurofibromatosis.

Mutation of GNAS1 gene results in autonomous function of bone through parathyroid hormone receptor; in skin through melanocyte-stimulating hormone receptor; in ovaries through the follicle-stimulating hormone receptor; and in the thyroid and pituitary gland through the thyroid and growth hormone receptors respectively.

Von Recklinghausens disease (Neurofibromatosis Type 1)

It is an autosomal dominant disorder characterized by multiple cutaneous lesions and tumors of the peripheral and central nervous system. Patients may present with Cafe-au-lait spots which are sharply defined light brown patches, Neurofibromas, Axillary freckling, Lisch nodules and skeletal abnormalities.

Diagnostic criteria for Neurofibromatosis 1 (NF1)
(NIH consensus development conference 1988)

1. 6 or more cafe´ au lait macules (.0.5 cm in children or .1.5 cm in adults)
2. 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
3. Axillary or groin freckling
4. Optic pathway glioma
5. 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
6. Bony dysplasia (sphenoid wing dysplasia, bowing of long bone, pseudarthrosis)
7. First degree relative with NF1.

Developmental

Nevi

Melanocytic nevi are benign tumors that arise as a consequence of melanocytic growth and proliferation. Skin is the most common site whereas intramucosal melanomas are more commonly seen with in the oral cavity. Genetic and environmental factors play an important role in the development of melanocytic nevi. Nevus cells are distinct biologically and morphologically from the melanocytes and appear as round, ovoid or spindled-shaped.
Based on evolution nevi can be classified into:
1. Junctional nevus
2. Compound nevus
3. Intradermal nevus

Oral nevi may present as a well-circumscribed macule with colour ranging from brown, bluish gray to black. An early melanoma may be mistaken for melanocytic nevi making biopsy mandatory for the definitive diagnosis. An aid in the differential diagnosis of nevi is that they are elevated from the mucosal surface where as melanotic macules and amalgam tattoos are usually flat. Vascular lesions can be mistaken for melanocytic proliferations, the former usually blanch with compression and aspiration of the lesion can be useful in differentiating a naevus from vascular lesion.

**Endocrine diseases**

**Addisons disease**

Primary adrenal insufficiency (Addison disease) occur as a result of auto immune destruction of Adrenal cortex resulting in diffuse dark pigmentation of skin and oral mucosa. The most common intra oral sites include lips, gingival, buccal mucosa, hard palate, and tongue. Pigmented lesions often precede skin manifestations.

**Chloasma**

Chloasma (Melasma) is characterised by symmetrically distributed brown macule on face. It is more common in females and occur in association with sunlight exposure, pregnancy (mask of pregnancy), use of birth control pills. Lesions are sharply delineated and it involves malar eminences, forehead, upper lip, and mandible.

**Neoplastic**

**Malignant melanoma**

Malignant melanoma is an aggressive tumor of melanocytes, accounting for 0.5% of all oral malignancies. Etiology remains unknown and possible risk factors include tobacco use and chronic mechanical irritation resulting from ill-fitting dentures. It can arise de novo from apparently normal mucosa and around 30% of cases are preceded by oral pigmentations for several months or even years. The colour may vary from brown, black, gray, purple, red and can even present as a depigmented lesion.

Oral mucosal melanomas are reported in four to seventh decade of life, more common in males and the most common sites include palate and gingiva. Oral mucosal melanoma behaves in a more aggressive fashion than cutaneous melanoma. Treatment involves radical surgical excision with clear margins. The prognosis for oral melanoma is poorer when compared with cutaneous lesions, and the overall 5-year survival rate is 15%. The best way to improve prognosis is early diagnosis.

**HIV associated pigmentation**

HIV associated pigmentation appear as asymptomatic, single or multiple, well or ill-defined, and light to dark brown macule of varying size and shape. It can affect any part of the oral mucosa and proposed etiopathogenesis includes HIV induced cytokine dysregulation and adrenocortical dysfunction in HIV positive subjects with low CD4+ T cell counts.

**Idiopathic pigmentation**

Idiopathic pigmentation includes Laugier-Hunziker pigmentation which is characterized by multi-focal pigmentation of the labial and buccal mucosa.

**Post inflammatory pigmentation**

It occurs as a result of inflammation or injury. They can be either hyper or hypo pigmentation and the most common examples are allergic reactions from insect bites or contact dermatitis, psoriasis or lichen planus etc.

**Drug induced pigmentation**

Drug induced hyperpigmentation is often idiopathic and it affects elderly individuals. Drugs like Minocycline, Levofloxacin, Rifampicin, Angiotensin II receptor antagonists, Calcium channel blockers are more commonly involved.

**Heavy metal exposure**

Heavy metals like lead, cadmium, mercury and zinc are responsible for hyperkeratosis and pigmentary changes.
**Smokers melanosis**

Smokers melanosis often affects the attached gingiva, hard palate, buccal mucosa, ventral surface of tongue and labial mucosa of tobacco smokers. Smoker’s melanosis does not require treatment, and disappearance have been reported after cessation of the smoking habit. Smokers melanosis frequently involves anterior gingiva and most often occurs in women who smoke and take oral contraceptives.

**Reactive pigmentation**

**Oral melanotic macule**

Oral melanocytic macule may present as a solitary melanocytic lesion predominantly involving labial mucosa, outer lip, gingiva and palate and frequently involves adult female patients.

**Oral melanocanthoma**

Oral melanocanthoma is a rare, benign pigmented lesion characterized by hyperplasia of spinous keratinocytes and dendritic melanocytes. It is believed to be reactive in origin and etiopathogenesis remains uncertain. Any mucosal site may be involved still buccal mucosa remains as the most common site. It may present as an ill-defined, rapidly enlarging, macule commonly observed in young individuals. Since it may mimic melanoma definitive diagnosis is obtained with histopathology and biopsy procedure itself can result in spontaneous regression of lesion.

**CONCLUSION**

Many pigmented lesions can be clinically diagnosed based on age of the patient, site, size, shape, colour of the lesion, history of previous surgery, trauma followed by biopsy along with other relevant clinical information. Above information is necessary for establishment of effective clinical manoeuvres for pigmented lesions of oral mucosa as it is crucial in the exclusion of possible malignancies. Pigmented lesions comprise a large component of those lesions which has a wide spectrum of histological appearances, most can be reported as simple benign nevi.

Any pigmented or partially pigmented oral lesion either macular or nodular should not be missed in the diagnosis. A small number will be typical malignant melanomas, although small in number are very important clinically and often results in both under & over diagnosis of melanoma. Therefore, it is important to approach all melanocytic lesions in a ritualistic & consistent manner to avoid potential serious diagnostic errors.

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