Pigmentary Disorders

Addison’s Disease

Etiology
• Adrenal cortical atrophy—85% idiopathic (?autoimmune)
• Oral manifestations due to secondary melanocyte stimulation by increased levels of adrenocorticotropic hormone (ACTH) or β-lipotropin

Clinical Presentation
• Brown macular pigmentation of local or diffuse quality
• Pigmentation usually seen in association with cutaneous bronzing, weakness, weight loss, salt craving, nausea, vomiting, hypotension

Diagnosis
• Confirmation of hypoadrenocorticism by plasma ACTH levels after challenge/stimulation
• Biopsy of mucosa shows melanosis

Differential Diagnosis
• Smoker’s melanosis
• Physiologic/ethnic pigmentation
• Heavy metal deposition/argyrosis
• Medication-related pigmentation
• Peutz-Jeghers syndrome

Treatment
• Management of underlying adrenal insufficiency by corticosteroid replacement therapy

Prognosis
• Good with replacement therapy
Amalgam Tattoo

Etiology
• Implantation or passive/frictional transfer of dental silver amalgam into mucosa

Clinical Presentation
• Gray to black focal macules, usually well defined, but may be diffuse with no associated signs of inflammation
• Typically in attached gingiva, alveolar mucosa, buccal mucosa
• Occasionally may be visible radiographically

Diagnosis
• Radiographs may be useful (intraoral film placement)
• Biopsy may be necessary if clinical diagnosis is in doubt or to rule out lesions of melanocytic origin

Differential Diagnosis
• Vascular malformation
• Mucosal nevus
• Melanoma
• Mucosal melanotic macule
• Melanoacanthoma

Treatment
• Biopsy or observation only

Prognosis
• Little clinical significance if untreated
Melanoacanthoma

Etiology
• A reactive and reversible alteration of oral mucosal melanocytes and keratinocytes
• Usually associated with local trauma

Clinical Presentation
• Unilateral dark plaque; rarely multiple, bilateral
• Most often noted among Blacks and other non-Caucasians
• Occurs more often in women than men by a ratio of 3:1
• History of trauma and local irritation
• Forms rapidly, most often on buccal/labial mucosa
• Asymptomatic melanotic pigmentation

Diagnosis
• Clinical history of rapid onset
• Histologic evaluation
  • Scattered dendritic melanocytes within spongiotic and acanthotic epithelium
  • Increased number of melanocytes along basal layer as single units

Differential Diagnosis
• Melanoma
• Drug-induced pigmentation
• Smoker’s melanosis
• Mucosal melanotic macule
• Mucosal nevus
• Amalgam tattoo

Treatment
• None after establishing the diagnosis
• Often resolves spontaneously

Prognosis
• Excellent
Mucosal Malignant Melanoma

Etiology
- Unknown
- Cutaneous malignant melanoma with relation to sun exposure or familial-dysplastic melanocytic lesions

Clinical Presentation
- Rare in oral cavity (< 1% of all melanomas) and sinonasal tract
- Most cases occur in those older than 30 years of age.
- Usually arises on maxillary gingiva and hard palate
- May exhibit early in situ phase: a macular, pigmented patch with irregular borders
- Progression to deeply pigmented, nodular quality with ulceration
- May arise de novo as a pigmented or amelanotic nodule
- Rarely may be metastatic to the oral cavity as a nodular, usually pigmented mass

Microscopic Findings
- Early stage: atypical melanocytes at epithelial–connective tissue interface, occasionally with intraepithelial spread
- Later infiltration into lamina propria and muscle
- Strict correlation to cutaneous malignant melanoma is not well established, although, as in skin, a similar horizontal or in situ growth phase often precedes the vertical invasive phase.
- Amelanotic forms may require use of immunohistochemical identification: S-100 protein, HMB-45, Melan-A expression

Diagnosis
- Biopsy
- High index of suspicion

Differential Diagnosis
- Mucosal nevus
- Extrinsic pigmentation
- Melanoacanthoma
- Kaposi’s sarcoma
- Vascular malformation
- Amalgam tattoo
- Mucosal melanotic macule
Treatment
• Surgical excision
  • Marginal parameters related to depth of invasion and presence of lateral growth
  • Wide surgical margins; resection (including maxillectomy) for large, deeper lesions
• Neck dissection in cases of deep invasion (< 1.25 mm)

Prognosis
• Generally poor for most oral malignant melanomas
• Less than 20% survival at 5 years in most studies
Mucosal Melanotic Macule and Ephelides

Etiology
• Most idiopathic, some postinflammatory, some drug-induced
• Multiple lesions suggest syndrome association, as follows:
  • Peutz-Jeghers syndrome
  • Laugier-Hunziker phenomenon
  • Carney’s syndrome
  • LEOPARD syndrome

Clinical Presentation
• Most in adulthood (fourth decade and beyond)
• Most are solitary and well circumscribed
• Lower lip vermilion border most common site, mostly in young women (labial melanotic macule)
• Buccal mucosa, palate, and attached gingiva also involved (mucosal melanotic macule)
• Usually brown, uniformly pigmented, round to ovoid shape with slightly irregular border
• Usually < 5 mm in diameter

Microscopic Findings
• Normal melanocyte density and morphology
• Increased melanin in basal cells and subjacent macrophages (mucosal melanotic macule)
• Increased melanin in basal cells with elongated rete pegs (ephelides)

Diagnosis
• Biopsy

Differential Diagnosis
• Melanoacanthoma
• Mucosal melanotic macule
• Congenital syndromes (Carney’s, Peutz-Jeghers, LEOPARD, Laugier-Hunziker)
**Treatment**
- Observation
- Biopsy for esthetics
- If increase in size or development of atypical signs occurs, macule should be removed to rule out malignant melanoma, particularly if on palate or alveolar mucosa.

**Prognosis**
- Excellent
Mucosal Pigmentation: Extrinsic (Drug or Metal Induced)

Etiology
- Occupational exposure—metals vapors (lead, mercury)
- Therapeutic—metal salt deposits (bismuth, cis-platinum, silver, gold); also nonmetal agents, such as chloroquine, minocycline, zidovudine, chlorpromazine, phenolphthalein, clofazimine, and others

Clinical Presentation
- Focal to diffuse areas of pigmentary change
- If heavy metals are the cause, a typical gray to black color is seen along the gingival margin or areas of inflammation.
- Palatal changes characteristic with antimalarial drugs and minocycline
- Most medications cause color alteration of buccal-labial mucosa and attached gingiva.
- Darkened alveolar bone with minocycline therapy (10% at 1 year, 20% at 4 years of therapy)

Diagnosis
- History of exposure to, or ingestion of, heavy metals or drugs
- Differentiation from melanocyte-related pigmentation by biopsy if necessary

Differential Diagnosis
- When localized: amalgam tattoo, mucosal melanotic macule, melanoacanthoma, mucosal nevus, ephelides, Kaposi’s sarcoma, purpura, malignant melanoma, ecchymosis
- When generalized: ethnic pigmentation, Addison’s disease
- If asymmetric, in situ melanoma must be ruled out by biopsy.

Treatment
- Investigation of cause and elimination if possible

Prognosis
- Excellent
Nevus

Etiology
- Unknown
- Lesion of melanocytic origin within mucosa and skin

Clinical Presentation
- Usually elevated, symmetric papule
- Pigmentation usually uniformly distributed
- Common on skin; unusual intraorally
- Palate and gingiva most often involved

Microscopic Findings
- Most are intramucosal (“dermal”)
- Blue nevi are deeply situated and are composed of spindled nevus cells.
- Other variants are rare; junctional and compound nevi (no dysplastic nevi occur orally)
- Nevus cells are oval/round and are found in unencapsulated nests (theques).
- Melanin production is variable.

Diagnosis
- Clinical features
- Biopsy

Differential Diagnosis
- Melanoma
- Varix
- Amalgam tattoo/foreign body
- Mucosal melanotic macule
- Kaposi’s sarcoma
- Ecchymosis
- Melanoacanthoma

Treatment
- Excision of all pigmented oral lesions to rule out malignant melanoma is advised.
- Malignant transformation of oral nevi probably does not occur.

Prognosis
- Excellent
Nevus of Ota

Etiology
• Idiopathic/congenital
• A proliferation of dermal melanocytes over a specific anatomic distribution

Clinical Presentation
• Macular, grayish blue discoloration of skin and mucosa over the distribution of the ophthalmic and maxillary branches of the trigeminal nerve
• Unilateral distribution
• Sclera on the involved side may be affected.

Microscopic Findings
• Diffuse unencapsulated proliferation of spindle-shaped melanocytes within dermis/submucosa, parallel to surface
• Pigment production may be florid.

Diagnosis
• Clinical presentation

Treatment
• None
• Cosmetic

Prognosis
• Excellent
Pigmentation Disorders: Drug Induced

Etiology
- Therapeutic drug-related tissue pigmentation
- Many drugs may cause change—see listing below

Clinical Presentation
- Macular mucosal discoloration (brown, gray, black)
- Palate and gingiva are most common sites affected
- In addition to mucosal changes, teeth in adults and children may be bluish gray owing to minocycline/tetracycline use (see “Tetracycline Staining” on page 138).

Microscopic Findings
- Most cases are due to increased melanin production. Some are related to the deposition of a drug complex or a metabolized drug.

Diagnosis
- History
- Clinical appearance

Differential Diagnosis
- Physiologic changes
- Smoker’s melanosis
- Mucosal melanotic macule

Treatment
- Drug withdrawal

Prognosis
- Good

Drugs Capable of Producing Tissue Pigmentation
- Antimalarials: chloroquine, mepacrine, quinidine, old-time antimalarials
- Antibiotics: tetracycline group, minocycline
- Antivirals: azidothymidine
- Phenothiazine: chlorpromazine
• Clofazimine
• Heavy metals: gold, mercury salts, silver nitrate, bismuth, lead
• Hormones: ACTH, oral contraceptives
• Cancer/chemotherapy drugs: busulfan, cyclophosphamide, cis-platinum
• Other: methyldopa
Pigmentation Disorders: Physiologic

Etiology
- Normal melanocyte activity

Clinical Presentation
- Seen in all ages
- Symmetric distribution over many sites, gingiva most commonly
- Surface architecture, texture unchanged

Diagnosis
- History
- Distribution

Differential Diagnosis
- Mucosal melanotic macule
- Smoking-associated melanosis
- Superficial malignant melanoma

Treatment
- None

Prognosis
- Excellent
Pigmentation Disorders: Smoker’s Melanosis

Etiology
- Melanin pigmentation of oral mucosa in heavy smokers
- May occur in up to 1 of 5 smokers, especially females taking birth control pills or hormone replacement
- Melanocytes stimulated by a component in tobacco smoke

Clinical Presentation
- Brownish discoloration of alveolar and attached labial gingiva, buccal mucosa
- Pigmentation is diffuse and uniformly distributed; symmetric gingival pigmentation occurs most often.
- Degree of pigmentation is positively influenced by female hormones (birth control pills, hormone replacement therapy).

Microscopic Findings
- Increased melanin in basal cell layer
- Increased melanin production by normal numbers of melanocytes
- Melanin incontinence

Diagnosis
- History of chronic, heavy smoking
- Biopsy
- Clinical appearance

Differential Diagnosis
- Physiologic pigmentation
- Addison’s disease
- Medication-related pigmentation (drug-induced pigmentation by chloroquine, clofazimine, mepacrine, chlorpromazine, quinidine, or zidovudine)
- Malignant melanoma

Treatment
- None
- Reversible, if smoking is discontinued

Prognosis
- Good, with smoking cessation
Tetracycline Staining

**Etiology**
- Prolonged ingestion of tetracycline or its congeners during tooth development
- Less commonly, tetracycline ingestion causes staining after tooth formation is complete: reparative (secondary) dentin cementum may be stained.

**Clinical Presentation**
- Yellowish to gray (oxidized tetracycline) color of enamel and dentin
- May be generalized or horizontally banded depending on duration of tetracycline exposure
- Alveolar bone may also be stained bluish red (particularly with minocycline use, 10% after 1 year and 20% after 4 years of therapy).

**Diagnosis**
- Clinical appearance and history
- Fluorescence of teeth may be noted with ultraviolet illumination.

**Differential Diagnosis**
- Dentinogenesis imperfecta

**Treatment**
- Restorative/cosmetic dental techniques

**Prognosis**
- Good