

# *Diseases of the Oral Cavity*

**Tri-Country Dermatology**

**Cuyahoga Falls, Ohio**

**AOCD-Oct 2015**

# Anatomy



# Fordyce Spots of the Lip Responding to Electrodesiccation and Curettage

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# Pigmented Lesions



# Melanocytic Macule

- **Presentation**: A slowly appearing solitary, brown or grayish brown macule, uniform in color and typically 2-15mm. \*lower lip, vermillion border, gingiva or palate.
- **Pathogenesis**: Benign hyperpigmentation. Occurring in approximately 3% of the general population. Common in patients of color, women, ~ 40 y/o.
- **Histo**: Increased melanin in melanocytes and keratinocytes of the basal layer; melanophages in the dermal papillae, indicating pigmentary incontinence, mild acanthosis without elongation of the rete ridges.
- **Treatment**: Serial photography to track any changes. When on the vermillion border is often a cosmetic concern. Biopsy or excision if any fear of melanoma or family history. The pigmentation is epidermal and will respond to laser treatments including ruby, alexandrite, pulsed dye and Q-switched Nd:YAG lasers



***Table 1* Drugs associated with oral mucosal pigmentation<sup>9,10</sup>**

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Antimalarials: quinacrine, chloroquine, hydroxychloroquine

Quinidine

Zidovudine (AZT)

Tetracycline

Minocycline

Chlorpromazine

Oral contraceptives

Clofazimine

Ketoconazole

Amiodarone

Busulfan

Doxorubicin

Bleomycin

Cyclophosphamide

5-Fluorouracil

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# Amalgam Tattoo

- **Presentation**: 0.5-1cm poorly defined or diffuse, solitary, slate-grey or blue-black macule. \*gingiva, alveolar ridge mucosa and buccal mucosa. \*adjacent to fillings or dental work containing silver filling material.
- **Pathogenesis**: Benign tattoo, present after dental work with silver filling material.
- **Histo**: Dark granules mainly along collagen bundles and around blood vessels.
- **Treatment**: No treatment is necessary unless for cosmetic reasons.



# Melanoma

- **Presentation**: Enlarging or spreading irregular plaque, darkly pigmented with multiple color variations, irregular borders, possible nodularity and ulceration. Typically on the hard palate or maxillary gingiva.
- **Pathogenesis**: rare in the oral cavity, <1% of all melanomas, men: 2:1, typically 5-6 decade or older. Very aggressive, vertical growth phase. Five year survival only 15%, average post diagnosis survival 2 years.
- **Histo**: Infiltration of connective tissue by atypical melanocytes, with or without melanin production. Confirmed by staining S100, HMB45, MART-1/Melan-A or MITF.
- **Treatment**: Wide excision, sentinel lymph node biopsy. Targeted therapies tyrosine kinase inhibitors may improve survival. Chemotherapy and radiation have little impact of course of disease.

# Hyperpigmentation of Oral Mucosa - Assoc Syndromes

- **McCune- Albright Syndrome:**
  - Sporadic somatic mutation , GNAS1 Gs subunit of adenylate cyclase, precocious puberty, café-au-lait pigmentation , endocrine abnormalities, pathologic fractures, skull sclerosis
- **Peutz-Jeghers Syndrome:**
  - AD, STK11/LKB1 gene mutation, encodes serine-threonine kinase tumor suppressor. Hyperpigmented macules on lip, fingers (starts infancy/childhood) , intussusceptions, intestinal polyposis. GI Malignancies
- **Carney Complex** ( LAMB or NAME Syndrome)
  - AD, PRKAR1A (protein kinase A regulatory subunit 1-alpha). Cardiac myxomas, endocrine abnormalities, pigmented skin lesions, psammomatous melanotic schwannoma
- **Laugier-Hunziker disease:**
  - Hyperpigmented macules of lips, oral cavity, genitals and longitudinal melanonychia
- **Addison's disease:**
  - Diffuse hyperpigmentation predominately over sun exposed regions. Weight loss, fatigue, vomiting and hypotension. Destruction of adrenocortical tissue via autoantibodies, trauma or infection

# Infections





# Angular Cheilitis (Perleche)

- **Presentation**: moist maceration, erythema, crusts or ulcers at the corners of the mouth; tenderness, burning, pruritus.
- **Pathogenesis**: ICD: anatomic-abnormal anatomy leading to exposure of irritant (loss of vertical dimension, improper fit of dental appliances; mechanical- eg, tobacco use, lip licking or drooling, dryness from mouth breathing; chemical factors- excessive saliva, burn, dental cleaning product. ACD (sunscreen, metals, fragrances, preservatives. Infection: ( secondary syphilis, *C. albicans*, *S. aureus*, strep, HSV): Nutritional deficiencies (iron, vitamin B2, B3, B6, B12, folic acid, Zn). Systemic causes (DM, HIV, SLE, secondary syphilis Downs syndrome, xerostomia causes: Sjogrens syndrome or medication induced xerostomia.
- **Histo**: ulcerations, spongiosis, infiltration of plasma cells and lymphocytes.
- **Treatment**: topical antifungals, abx, avoidance of irritation/allergen. If failed therapy, consider investigating systemic cause or nutritional deficiency.

Park KK, Brodell RT, Helms SE. Angular cheilitis, part 2: nutritional, systemic, and drug-related causes and treatment. *Cutis*. 2011 Jul;88(1):27-32.

Park KK, Brodell RT, Helms SE. Angular cheilitis, part 1: local etiologies. *Cutis*. 2011 Jun;87(6):289-95.

Sharon V, Fazel N. Oral candidiasis and angular cheilitis. *Dermatol Ther*. 2010 May-Jun;23(3):230-42.





# Oral Candidiasis (Thrush)

- **Presentation:** Creamy white lesions on the oral mucosa → gentle scraping shows erythematous mucosal surface.
  - acute pseudomembranous candidiasis; chronic erythematous candidiasis; acute erythematous candidiasis; and chronic hyperplastic candidiasis. Dx mostly clinical but may be confirmed through microscopic identification of *Candida* in the oral samples and/or isolation in culture.
- **Pathogenesis:** is normal flora but broad spectrum antibiotics may trigger thrush, diabetes, malnourishment, debilitation in elderly is common, -immunosuppressed individuals
- **Histo:** + *Candida* hyphae, an inflammatory cell infiltrate is invariably present within the lamina propria together with marked variations in epithelial thickness
- **Treatment:** single dose of fluconazole 150mg is effective for many adults. Immunosuppressed pts: 200mg/day starting dose, itraconazole 200mg/day for 5-10 days, or terbinafine 250mg/day. Oral antiseptic and antibacterial rinses such as Chlorhexidine or Hexetidine. Nystatin at doses of 100 000 IU/ml [5ml 4 times daily] and amphotericin b at 50mg [5ml 3 times per day]. Miconazole gel or buccal mucosal tablet.

Coronado-Castellote L, Jiménez-Soriano Y. Clinical and microbiological diagnosis of oral candidiasis. J Clin Exp Dent. 2013 Dec 1;5(5):e279-86.

García-Cuesta C, Sarrion-Pérez MG, Bagán JV. Current treatment of oral candidiasis: A literature review. J Clin Exp Dent. 2014 Dec 1;6(5):e576-82.

Williams D, Lewis M. Pathogenesis and treatment of oral candidosis. J Oral Microbiol. 2011 Jan 28;3. **Presentation:** Creamy white lesions on the oral mucosa



# Median Rhomboid Glossitis (MRG)

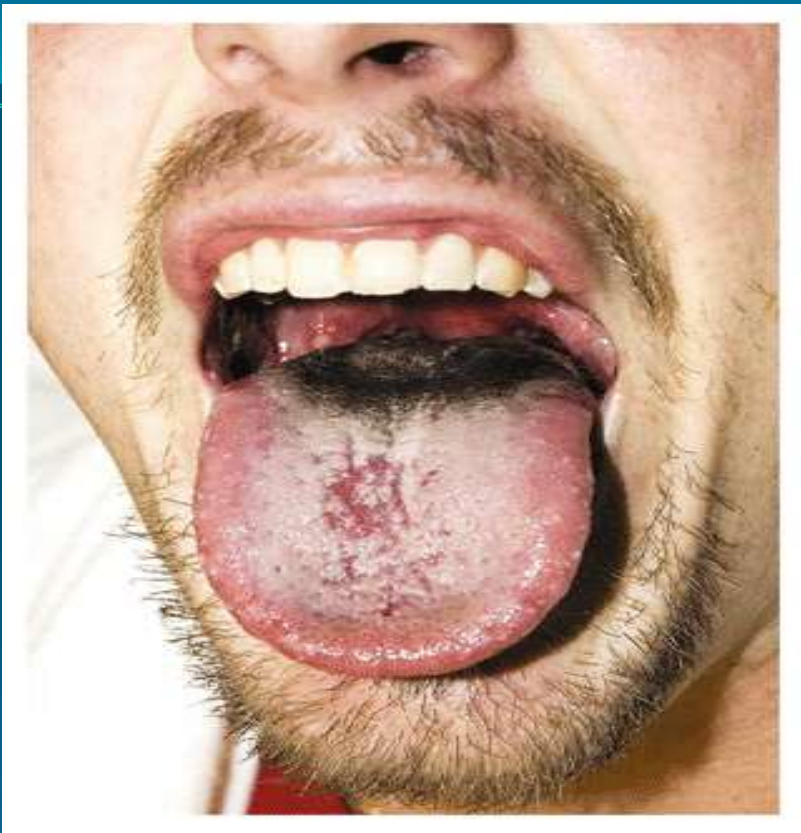
- **Presentation**- Shiny, smooth, red, diamond shaped or oval shaped elevation on midline dorsal aspect of tongue. Sessile appearance consistent with denuded papillae; w/ focal areas of residual papillae. Classic rhomboid appearance is most common.
  - AKA central papillary atrophy; happens in 1% of adults, with M > F 3:1
- **Pathogenesis**: abnormal fusion of posterior portion of the tongue; infection w/ *C. albicans*.
- **Histo**: absence of papillae with epithelium that can range from atrophic to hyperplastic. The underlying stroma usually contains an inflammatory infiltrate. Fungal stains, such as Gomori's methenamine silver, may be used to demonstrate *Candida*, but they are often unnecessary, as the organisms can frequently be seen with H&E.
- **Treatment**- Same as for thrush: Topical antifungals, such as nystatin (Mycostatin, generics) or clotrimazole (Mycelex, generics).





# Chronic Mucocutaneous Candidiasis (CMC)

- **Presentation:** chronic mucosal, skin and nails - *Candida*. < 6 years old. Oral lesions are diffuse, and palate and lip fissures. Dystrophic nails, and may or may not be accompanied by endocrinopathy, hyper IgM, HIV infection.
- **Pathogenesis:** familial or sporadic, early or adult onset (especially with thymoma). The mechanism of CMC is unclear.
  - CMC with endocrinopathy → APECED (Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dysplasia) syndrome, a familial recessive inheritance gene defect associated with the autoimmune regulator, *AIRE* found on locus 21q22.3.
  - Iron deficiency and/or a selective defect in the ability of the cellular immune response to clear *C. albicans* infection is usually thought to be associated with CMC.
- **Histo:** The most important histological findings showed: (1) epithelial hyperplasia (acanthosis) with thick layer of keratinization; (2) superficial micro-abscesses, intraepithelial; (3) inflammatory cells (mainly neutrophils) throughout the layer of the epithelium; (4) intracellular edema adjacent to the micro-abscesses; and (5) large amounts of hyphae of *C. albicans* in the upper layer of the epithelium under the PAS staining.
- **Treatment:** PO fluconazole, itraconazole or ketoconazole, or nystatin.



N ENGL J MED 357:23 WWW.NEJM.ORG DECEMBER 6, 2007



N ENGL J MED 354:1 WWW.NEJM.ORG JANUARY 5, 2006

# Black Tongue (Lingua Villosa Nigra)

- **Presentation:** Black, brown, green, or yellow patches on dorsum of tongue w/ hairlike filaments.
- **Pathogenesis:** smoking, oral Abx use or psychotropic drug use and presence of *C. albicans* on the tongue.
- **Histo:** Hairs are benign hyperplasia of filiform papilla from retention of long conical filaments of orthokeratotic and parakeratotic cells.
  - Acanthosis, parakeratosis, irregular projections of keratin and vacuolated keratinocytes with Epstein- Barr present within them
- **Treatment:** Toothbrush to scrub off projections with 1-2% hydrogen peroxide
  - Application of Retin-A gel or 40% aqueous solution of urea or papain (meat tenderizer) then brush off projections.
  - Eliminate causative agent if known.



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:  
*Fitzpatrick's Dermatology in General Medicine*, 7th Edition: <http://www.accessmedicine.com>  
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**A**

Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:  
*Fitzpatrick's Dermatology in General Medicine*, 7th Edition: <http://www.accessmedicine.com>

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# Herpes Simplex

- **Presentation:** numerous discrete, small vesicles in clusters (primary) or singly (secondary) on palate, gingiva or tongue or lips on one ½ of body (following a dermatome). Grouped vesicles rupture rapidly and form punctate erosions with a red base. Will be cyclical in immunocompetent individual: outbreak lasts approx 2 weeks then resolves; can get new outbreak with trigger as frequently as Qmonth.
  - **Ddx:** oral VZV, herpangina and oral aphthosis. The latter two involve nonattached mucosa whereas VSV typically involves mucosa fixed to bone.
- **Pathogenesis:** Herpes labialis is usually due to HSV1>HSV2.
  - Dx is usually mainly clinical and w/ hx. Smears from base with Wright stain will show multinucleate giant cells. Immunofluorescent tests and viral cx are confirmatory.
- **Histo:** acantholysis w/ solitary keratinocytes within the blister cavity. Nuclear changes of viral infection: *margination* of the nuclear chromatin, *multinucleation* and *moulding*.
- **Treatment:** Valacyclovir, 2 g twice in 1 day taken during the prodromal stage of herpes labialis, reduces the episode duration and time to healing. Acyclovir, 400 mg, taken 5 times a day for 5 days, decreases the pain duration and healing time to loss of crust. Both PO Valacyclovir and Acyclovir reduce outbreak by 1 day.
  - New buccal tablet Sitavig (Oral acyclovir 50mg x 1 PO) also reduces outbreaks by 1 day & decreased freq of outbreaks.
  - Topical penciclovir 1%, acyclovir 5% decrease the duration of pain and healing time.
  - The best prophylaxis for herpes labialis is PO valacyclovir 500 mg daily; it reduces the frequency and severity of attacks. SPF may be effective in sunlight-induced recurrence

Chon, T, and Nguyen, L. What are the best treatments for herpes labialis? *J Fam Pract.* 2007 July;56(7):576-578.

Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007 Mar;103 Suppl:S12.e1-18.

Bieber et al. Efficacy and safety of aciclovir mucoadhesive buccal tablet in immunocompetent patients with labial herpes (LIP Trial): a double-blind, placebo-controlled, self-initiated trial. *J Drugs Dermatol.* 2014 Jul;13(7):791-8.



<http://derm.s.net>

# Heck's Disease

- **Presentation:** ++ pinkish plaques on the oral mucosa & lower lip, gingiva, tongue or buccal mucosa
  - HPV 13, 32 (in adults)
- **Pathogenesis:** HPV induced focal epithelial hyperplasia (FEH).
  - Assoc to malnutrition, poor hygiene genetic factors.
- **Histo:** Mitosoid cells: virus-altered keratinocytes w/ nuclei resembling mitotic figures (pathognomonic for Heck's); also see focal parakeratosis, hyperkeratosis, acanthosis, verrucous proliferation and marked papillomatosis, hyperplasia of basal cells, and isolated perinuclear cellular vacuolization (koilocytosis).
- **Treatment:** Treatment of FEH is not always indicated as the lesions are asymptomatic and often regress spontaneously, but can be removed if are being traumatized.





Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:  
*Fitzpatrick's Dermatology in General Medicine*, 7th Edition: <http://www.accessmedicine.com>

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# Kaposi's Sarcoma

- **Presentation:** Oral KS (OKS) most often affects the hard and soft palate, gingiva, and dorsal tongue with plaques or tumors that can be non-pigmented, brownish-red, or violaceous. It may develop anywhere in the oral cavity, including the masseter muscle, uvula, and oropharynx. Tongue KS → mid-dorsal aspect of the tongue at the junction of the anterior two-thirds and posterior third.
  - Progression from patches of OKS to plaque or nodular forms is associated with worsening of immunosuppression.
  - Exophytic KS can become superinfected by oral microflora, present w/ problems w/tooth mobility and disfigurement if it is visible, and may interfere with mastication, the placement of oral prostheses, and oral hygiene
    - DDX: OKS needs to be distinguished clinically from other entities, including pyogenic granuloma, hemangioma, bacillary angiomatosis, and gingival enlargement caused by CsA, a drug frequently used in recipients of organ transplantation.
    - 4 known variants of KS: epidemic or AIDS-associated KS, endemic or African KS, iatrogenic post-transplantation KS, and Mediterranean or classic KS (CKS). CKS mostly affects elderly Eastern European Jewish or Mediterranean men (male/female ratio: 10-15:1). Lesions occur mostly on the skin of the lower limbs and, more rarely, in internal organs.
- **Pathogenesis:** Involvement of the oral cavity may be seen in all variants but is most common with AIDS-KS. HHV8, a herpesvirus associated with neoplastic diseases, which is postulated to be transmitted via the saliva, has been found in all pts with KS.
- **Histo:** depending on the stage (patch, plaque or nodular), but in general: spindle cell proliferation, lymphocytes and plasma cells, incomplete vascular slits, and extravasated erythrocytes and hemosiderin-laden macrophages. These microscopic features may not be as evident in early patches but develop with clinical progression into nodules.

# Kaposi's Sarcoma

- **Treatment:** KS is an opportunistic tumor and the restoration of immunity is the best way to treat sarcoma in organ transplant recipients and in AIDS-associated KS (anti-retroviral therapy). In CKS, immunosenescence is not controllable and cannot therefore be targeted by treatment
  - Focal OKS may be surgically excised when lesions are accessible; however, large or diffuse lesions are best managed by debulking rather than full excision because of the potential for extensive residual defects and poor healing.
  - Radiotherapy, chemotherapy, interferon alfa, and surgery: in HIV-positive patients → HAART or with a combination of this therapeutic approach
  - Intralesional vincristine, intralesional interferon alfa-2, imiquimod, and nicotine patches
  - Systemic cytotoxic agents are usually prescribed to patients not responding to HAART and/or with widespread mucocutaneous and visceral disease. Several drugs, such as vincristine, vinblastine, etoposide, bleomycin, docetaxel, and paclitaxel, can be administered

Treatments for classic Kaposi sarcoma: A systematic review of the literature. Régnier-Rosencher, Elodie et al. Journal of the American Academy of Dermatology , Volume 68 , Issue 2 , 313 - 331

Oral HIV-associated Kaposi sarcoma: A case report. Journal of the American Academy of Dermatology , Volume 72 , Issue 5 , AB55  
Pittore B, Pelagatti CL, Deiana F, et al. Isolated Kaposi Sarcoma of the Tonsil: A Case Report and Review of the Scientific Literature. Case Reports in Otolaryngology. 2015;2015:874548.

Grayson W, Pantanowitz L. Histological variants of cutaneous Kaposi sarcoma. Diagnostic Pathology. 2008;3:31  
Fatahzadeh M, Schwartz RA. Oral Kaposi's sarcoma: a review and update. Int J Dermatol. 2013 Jun;52(6):666-72

Atypia

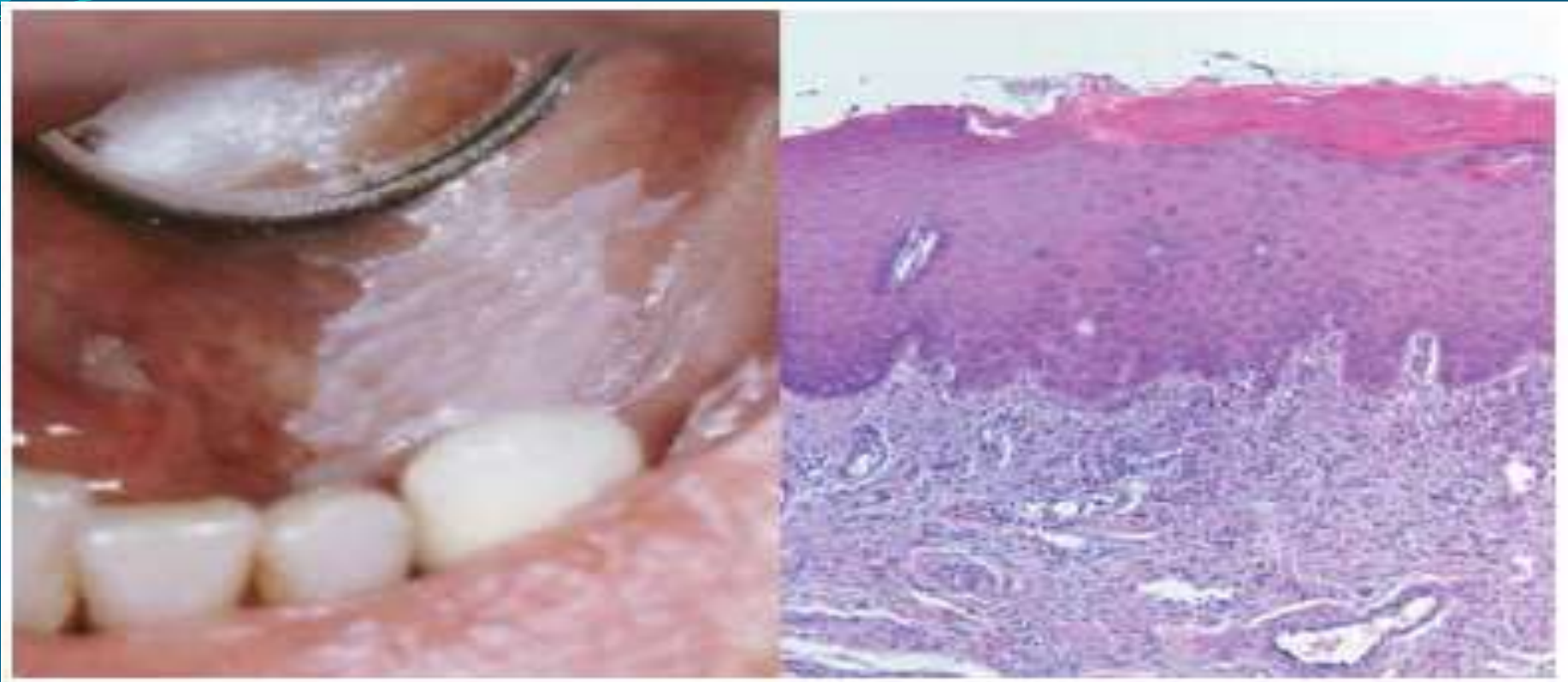


Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ:  
*Fitzpatrick's Dermatology in General Medicine*, 7th Edition: <http://www.accessmedicine.com>  
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# Actinic Cheilitis

- **Presentation:** Lower lip → scaly, fissured, atrophic sometimes eroded and swollen.
- **Pathogenesis:** Inflammatory reaction of the lips due to chronic excessive sun exposure over many years. Propensity for development of leukoplakia or SCC.
- **Histo:** hyperplasia, acanthosis or atrophy of the epithelium, thickening of the keratin layer, and/or dysplasia, which may range from mild to severe, + solar elastosis
- **Treatment:** Avoid sun exposure and use of SPF. Cryosurgery may be effective. If diffuse, may use topical 5-FU, imiquimod or photodynamic therapy. Treatment with CO<sub>2</sub> or Er: YAG laser, dermabrasion or electrodessication may be needed for severe disease.





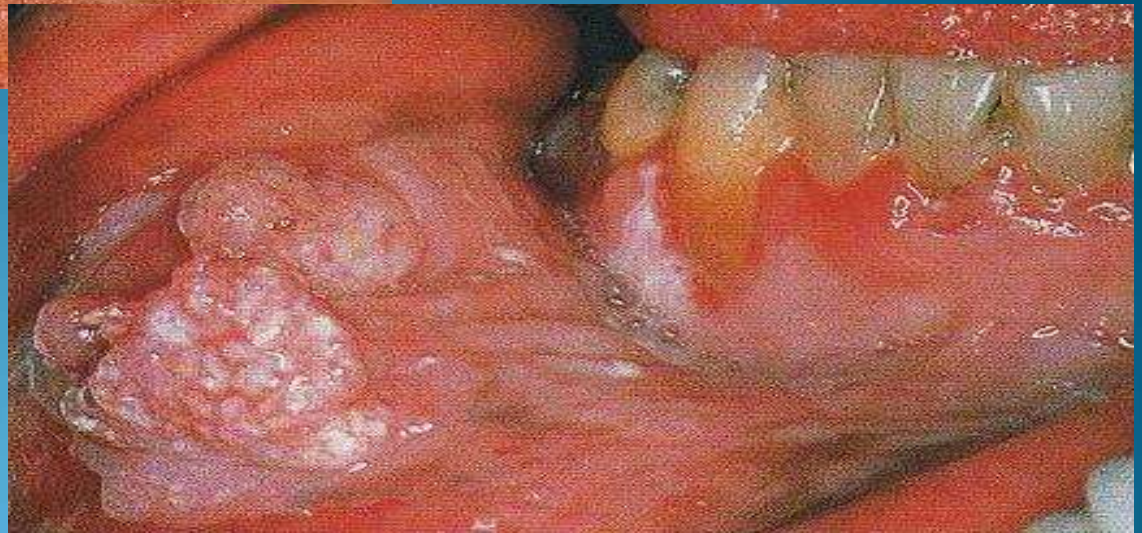
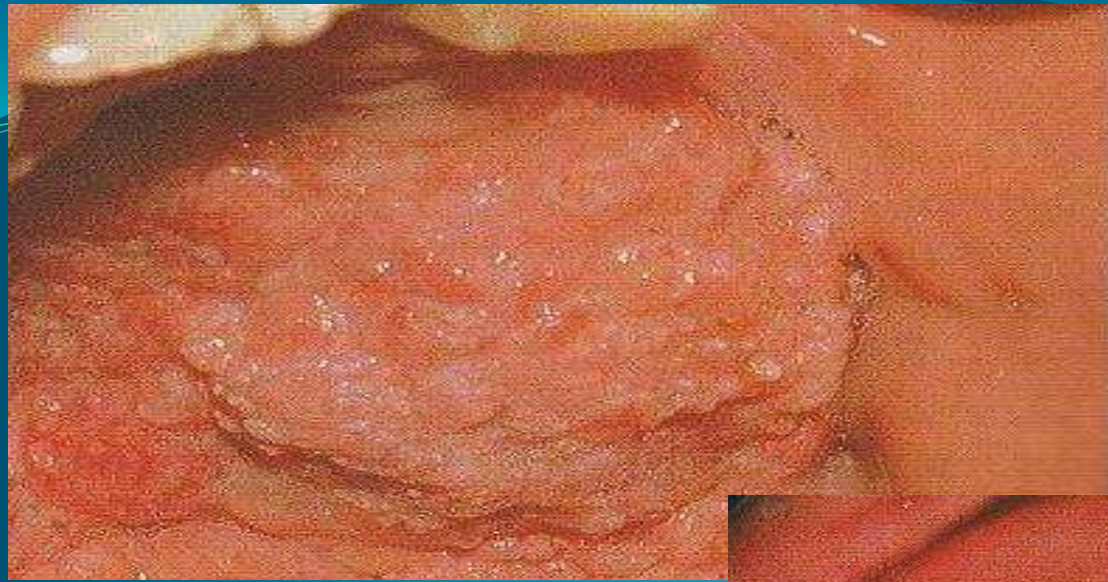


# Leukoplakia

- **Presentation:** Whitish thickening of the epithelium of the mucous membranes. Attempts to remove → bleeding. It can also be thick rough and elevated plaque. Lips, gums, cheeks and edges of the tongue. Mostly common in males over age 40.
- **Pathogenesis:** From chronic irritation with little chance of conversion into precancerous form (smoking, smokeless tobacco, alcohol, poorly fitted dentures). Premalignant leukoplakia presents in 10-20% of leukoplakia. Viral induced variant called oral hairy leukoplakia occurs primarily in pts with AIDS.
  - High-grade dysplasia had significantly higher malignant incidence than low-grade dysplasia. Four factors including patient aged >60 years, lesion located at lateral/ventral tongue, non-homogenous lesion, high-grade dysplasia were independent significant indicators for Oral Leukoplakia malignant transformation
- **Histo:** orthokeratosis or parakeratosis with minimal inflammation or varying degrees of dysplasia; loss of polarity, increase # mit figures, nuclear pleomorphism, loss of differentiation.
- **Treatment:** Recommend complete removal if dysplastic via surgery or destruction. Fulguration, simple excision, cryotherapy and CO2 laser ablation are all effective methods of treatment. Elimination of irritant if known.

Park MW, Cho YA, Kim SM, Myoung H, Lee JH, Lee SK. Focal epithelial hyperplasia arising after delivery of metal-ceramic fixed dental prosthesis. J Adv Prosthodont. 2014 Dec;6(6):555-8

Liu W, Shi LJ, Wu L, Feng JQ, Yang X, Li J, Zhou ZT, Zhang CP. Oral cancer development in patients with leukoplakia--clinicopathological factors affecting outcome. PLoS One. 2012;7(4)



# Condyloma Accuminata (CA)

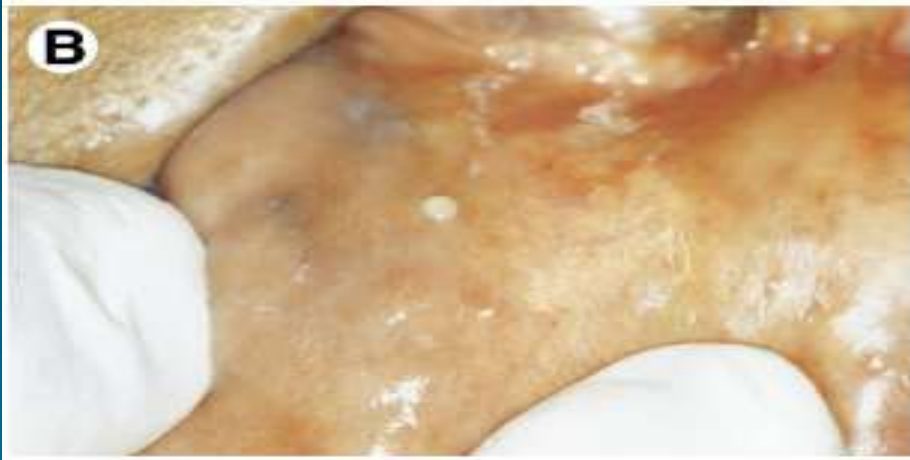
- **Presentation:** any size, can be sessile, papillomatous, exophytic, hemorrhagic, pedunculated
  - **Ddx:** VV, oral bowenoid papulosis and oral mucosal lesions of Cowden's (multiple hamartoma) syndrome.
- **Pathogenesis:** sexual transmission of HPV types 6, 11, and 32.
- **Histo:** benign acanthoma w/ papillomatous projections has a parakeratotic surface w/ a compact stratum corneum, coarse hypergranulosis, and vacuolated keratinocytes; w/ rare koilocytosis.
- **Treatment:** For oral mucosa: surgical excision, which may be cryosurgery, scalpel excision, ED&C, or laser ablation. There are other treatments for CA when non-mucosal sites are involved (5-fu, TCA, imiquimod, etc).

Breen, E, et al. Condylomata acuminata (anogenital warts) in adults. UpToDate. Last updated Apr 30, 2015. Accessed Aug 2, 2015.

Ozdamar SS, Ozdamar O, Kucukodaci Z. Giant intraoral condyloma accuminatum lesion coexisting with genital condyloma. Pak J Med Sci. 2014 Sep;30(5):1143-6.

Gupta RR, Puri UP, Mahajan BB, Sahni SS, Garg G. Intraoral giant condyloma accuminatum. Indian J Dermatol Venereol Leprol. 2001 Sep-  
O: 37(5):294-5

# Miscellaneous diseases of the lips



# Cheilitis Glandularis

- **Presentation**: Pinpoint red macules, Macrocheilia due to mucous gland swelling +/- purulent discharge from the ducts.
  - Rare inflammatory condition of the minor salivary glands, usually affecting the lower lip.
  - It carries a risk of (18% to 35%) malignant transformation to squamous cell carcinoma.
- **Histo**: Salivary duct ectasia, mucous accumulation, chronic inflammation and fibrosis
- **Treatment**: Vermilionectomy (lip shave) is the treatment of choice. Intralesional steroids, minocycline and tacrolimus ointment are the other treatment modalities.



# Cheilitis Granulomatosa

- **Presentation**: Persistent, non-tender lip swelling progressing to chronic enlargement
- **Pathology**: Subepithelial non-caseating granulomas
  - Melkersson-Rosenthal Syndrome: triad of recurrent/chronic orofacial edema, facial nerve palsy, and fissured tongue
  - Evaluation for dental/sinus inflammation, Crohn's disease, sarcoidosis, leprosy, tuberculosis, chronic granulomatous disease, and possibly deep fungal infections should be considered
- **Treatment**: IL corticosteroids 10mg/cc, alternatively oral prednisone, hydroxychloroquine or minocycline



# Diseases of the tongue



# Atrophic Glossitis

- **Presentation**: Smooth, red glistening tongue that is often painful w/ loss of filiform papillae
- **Pathogenesis**: May be caused by:
  - Nutritional deficiencies (vitamin E, riboflavin, niacin, vitamin B 12 , iron) – Hunter Glossitis if B12
  - Infections (viral, candidiasis, tuberculosis, syphilis)
  - Trauma (poorly fitting dentures)
  - Irritation of the tongue from toothpaste, medications, alcohol, tobacco, citrus
  - Lichen planus, pemphigus vulgaris, erythema multiforme
- Obtain CBC, B12 level and KOH scraping
- **Treatment** directed at underlying disease. Biopsy may be needed to rule out neoplasm. Also, emphasize avoidance of primary irritants such as hot foods, spices, tobacco, and alcohol.



# Geographic Tongue

- **Presentation**: Well-demarcated ringed or gyrate erythema with whitish rim typically involving dorsal and lateral tongue; usually asymptomatic
  - benign migratory glossitis
  - Irregular shaped swollen patches often look like maps
  - Noted in increased frequency in psoriasis
  - May be a manifestation of pustular psoriasis, allergy, hormonal disturbance, juvenile diabetes, Reiter syndrome, Down syndrome, nutritional deficiencies, and psychological stress, fissured tongue and LP.
  - ? genetic predisposition has also been suggested
  - A geographic tongue in an otherwise healthy person may indicate a propensity to develop generalized pustular psoriasis
- **Histo**: shows marked transepidermal neutrophil migration with the formation of spongiform pustules in the epidermis and an upper dermal mononuclear infiltrate.
- **Treatment**: Tretinoin 0.025% gel or 0.1% solution applied to the tongue twice daily, usually clears the lesions in less than 1 week.

Glossitis with linear lesions: An early sign of vitamin B12 deficiency Graells, Jordi et al. JAAD , Volume 60 , Issue 3 , 498 – 500

Assimakopoulos D, Patrikakos G, Fotika C, Elisaf M. Benign migratory glossitis or geographic tongue: an enigmatic oral lesion. Am J Med. 2002 Dec

15;113(9):751-5



# Fissured Tongue

- **Presentation**: Benign, non-painful furrows on dorsum of tongue with “corrugated appearance” (Scrotal tongue)
  - Also called lingua plicata
- May be associated with Melkersson-Rosenthal syndrome and Down Syndrome, pachyonychia congenita, pemphigus vegetans, Cowden syndrome. Usually occurs together with geographic tongue and more commonly present in patients with psoriasis
- **Treatment**: Maintenance of oral hygiene with mouthwashes



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# Amyloidosis

- **Presentation**: Macroglossia (firm, rubbery, smooth yellow-white nodules) may be the first manifestation with speech, chewing, and swallowing difficulties.
- **Pathogenesis**: Progressive extracellular deposition of amyloid within the suprahyoid muscles
  - Almost universally due to systemic disease
  - May be associated with blood dyscrasias, multiple myeloma or dialysis related lesions
  - Must rule out systemic disease with abdominal fat biopsy or rectal biopsy
- **Histo**: eosinophilic amorphous material on H&E with apple green birefringence under Congo Red staining and polarized light
- **Treatment**: dependent on overall organ involvement and presence of ROS element

Pentenero M, Davico Bonino L, Tomasini C, Conrotto D, Gandolfo S. Localized oral amyloidosis of the palate. *Amyloid* [serial online]. March 2006;13(1):42-46. Available from: Academic Search Premier, Ipswich, MA. Accessed July 26, 2015.

Xavier S, Filho I, Müller H. Macroglossia secondary to systemic amyloidosis: Case report and literature review. *ENT: Ear, Nose & Throat Journal* [serial online]. June 2005;84(6):358-361. Available from: Health Source - Consumer Edition, Ipswich, MA. Accessed July 26, 2015.

# Inflammatory/reactive conditions



# Oral Lichen Planus (LP)

- **Presentation**: “Classic” reticulate white lesions of the buccal mucosa
  - 80% in the buccal mucosa, 65% in the tongue, 20% lips, <10% seen in floor of mouth and palate
  - Malignant transformation → SCC
- **Pathogenesis**: T cell-mediated mucocutaneous disease of unknown etiology
- **Histo**: Band-like subepithelial mononuclear infiltrate consisting of (CD8+) T cells and histiocytes, increased numbers of intraepithelial T cells, and degenerating basal keratinocytes that form colloid bodies
  - Variable :parakeratosis, acanthosis, and sawtooth rete

# Oral Lichen Planus

- **Treatment**: Eliminate local and exacerbating factors
  - Superpotent steroids in Orabase or gel form
  - Systemic therapy: Thalidomide, metronidazole, griseofulvin, and hydroxychloroquine, some retinoids, and corticosteroids
  - Surgical excision: Reserved to remove high risk dysplastic areas
  - Cryotherapy
  - CO2, ND:YAG laser, PUVA

Gupta S, Jawanda MK. Oral Lichen Planus: An Update on Etiology, Pathogenesis, Clinical Presentation, Diagnosis and Management. *Indian Journal of Dermatology*. 2015;60(3):222-229. doi:10.4103/0019-5154.156315.

Krupaa RJ, Sankari SL, Masthan KMK, Rajesh E. Oral lichen planus: An overview. *Journal of Pharmacy & Bioallied Sciences*. 2015;7(Suppl 1):S158-S161doi10.4103/0975-7406.155873



# Erosive LP of the Gingiva

- **Presentation**: Diffuse erythematous areas that may or may not be interspersed with desquamative and ulcerated foci
  - hyperkeratotic radiating striae found at the periphery of the erosive regions
- **Pathogenesis**: T-cell–mediated autoimmune disease in which autotoxic CD8<sup>+</sup> T cells trigger apoptosis of oral epithelial cells
  - Malignant transformation: Higher rate of SCC seen in the non-reticular varieties (i.e. atrophic, plaque, and erosive forms)

# Erosive LP of the Gingiva

- **Histo**: H&E and DIF to exclude other autoimmune disease: Basal cells vacuolization, dense lymphocytic infiltrate at epithelium connective tissue junction with serrated rete ridge pattern
  - Ulcerative form of LP may not show the characteristic histological and DIF features of oral LP so a bx confined to an ulcerative lesion only r/o epithelial dysplasia or carcinoma
  - A bx of the ulcerative form should include adjacent areas featuring other forms of the disease



# Erosive LP of the Gingiva

- **Treatment:** Aggressive oral hygiene
  - Topical steroids - Good environment for *C. albicans*
    - Fluocinonide, Clobetasol, Betamethasone, Triamcinolone acetonide 0.1%, mouthrinse or Orabase paste
  - Topical tacrolimus
  - Systemic therapies: Hydroxychloroquine, azathioprine, mycophenolate, dapsone, corticosteroids
  - Topical and systemic retinoids or PUVA

Sugerman PB, Satterwhite K, Bigby M. Autocytotoxic T-cell clones in lichen planus. *Br J Dermatol.* 2000 Mar. 142(3):449-56. [Medline].

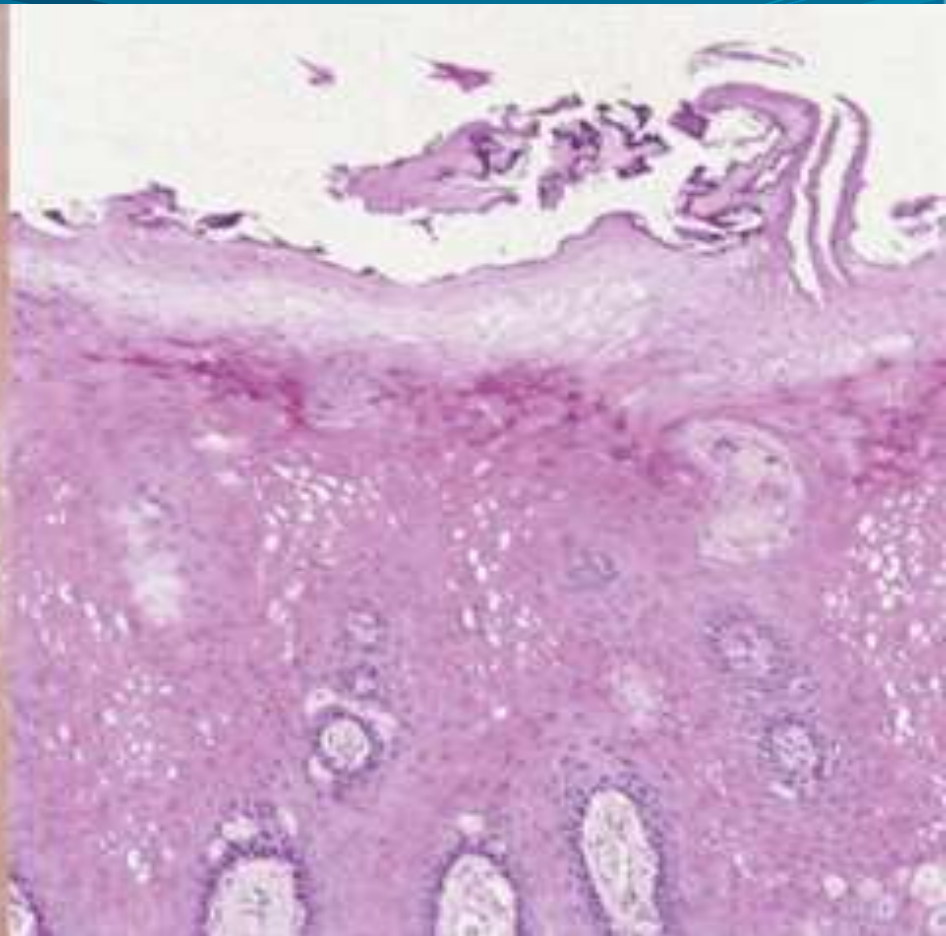
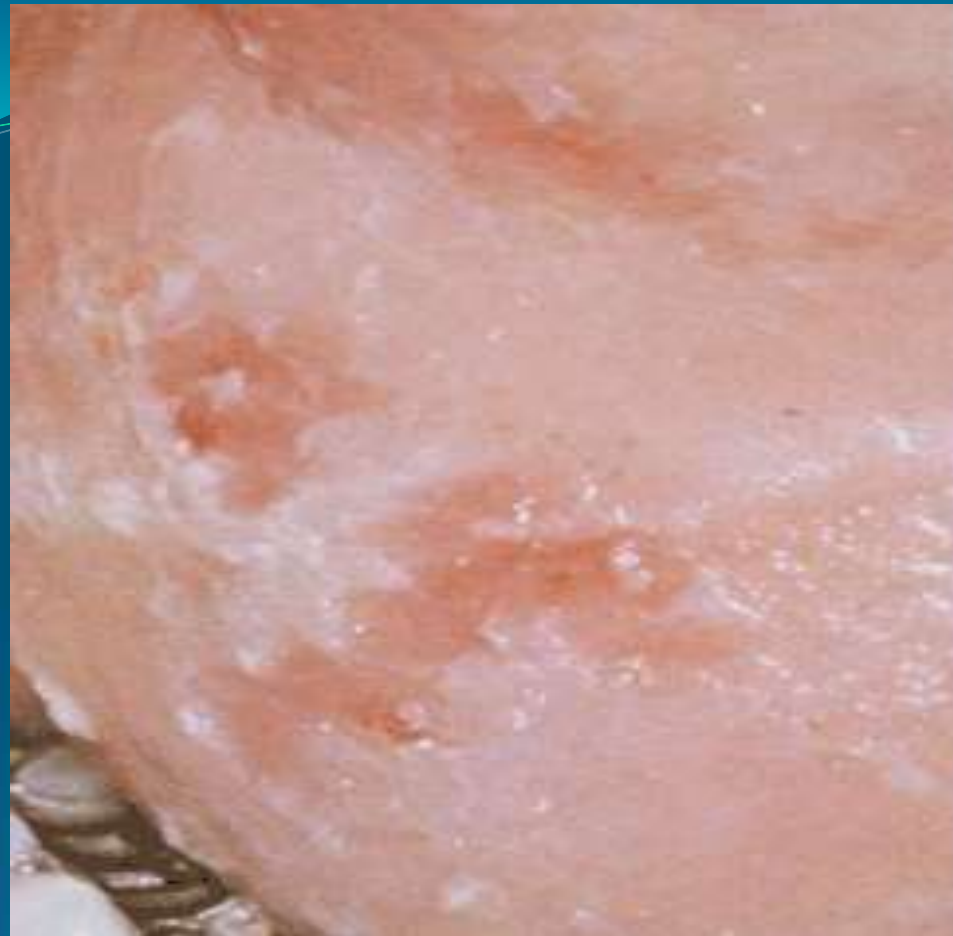
Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med.* 2002. 13(4):350-65. [Medline].

Shan J, Ma JM, Wang R, Liu QL, Fan Y. Proliferation and Apoptosis of Peripheral Blood Mononuclear Cells in Patients with Oral Lichen Planus. *Inflammation.* 2012 Nov 8. [Medline].

Ambika Sharma, Chakshu Aggarwal, Vijay P. Mathur, and Divesh Sardana, "Severe Gingival Enlargement with Coexisting Erosive Lichen Planus in Severe Chronic Periodontitis Patient," Case Reports in Dentistry, vol. 2015, Article ID 538538, 6 pages, 2015. doi:10.1155/2015/538538

Al-Hashimi I, Schifter M, Lockhart PB, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007 Mar;103 Suppl:S25.e1-12

Kalmar JR. Diagnosis and management of oral lichen planus. *J Calif Dent Assoc.* 2007 Jun;35(6):405-11

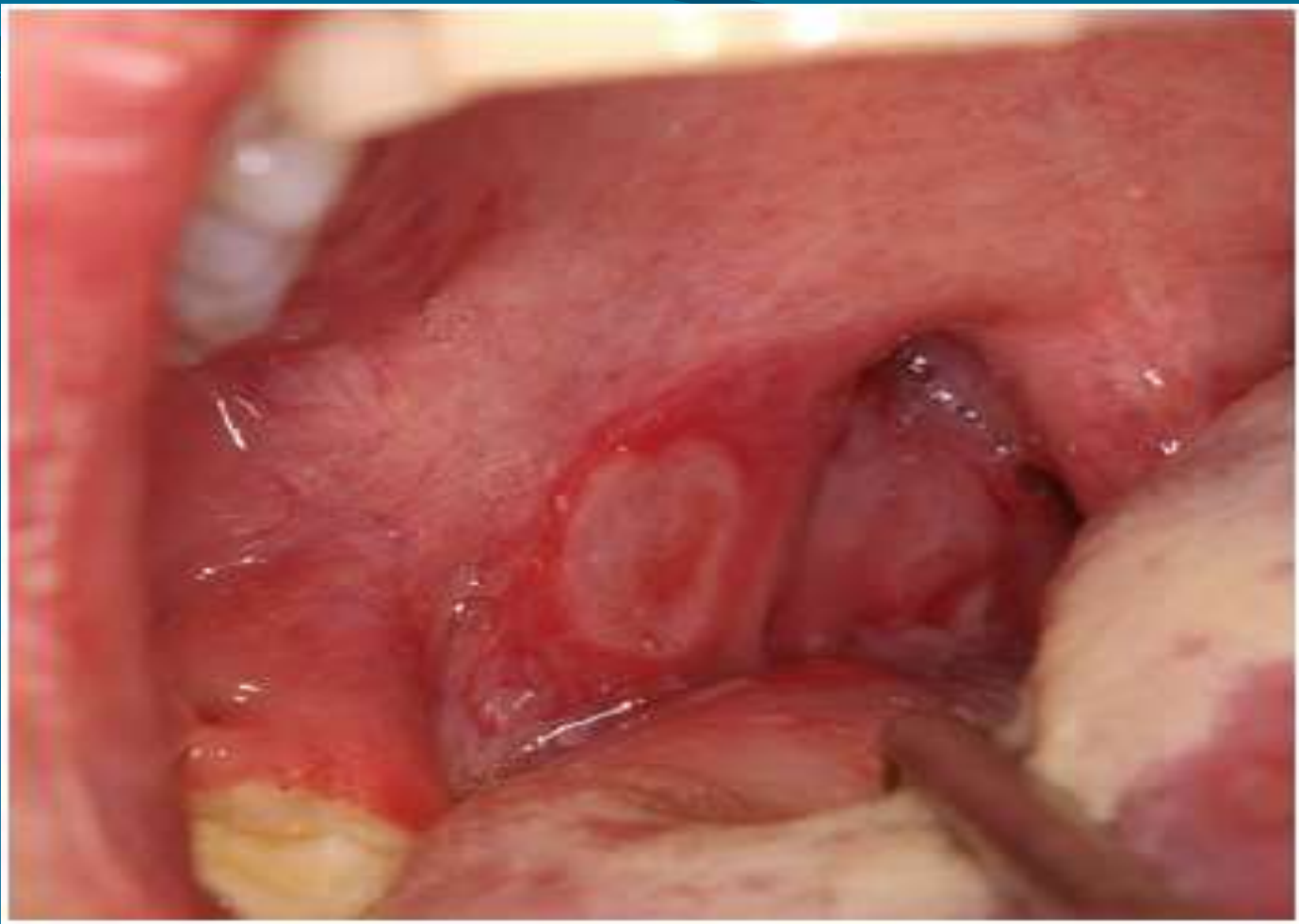


# Morsicatio Buccarum, “Oral Frictional Hyperkeratosis

- **Presentation**: Shaggy white plaque on the buccal mucosa
- **Pathogenesis**: Chronic irritation from biting
- **Histo**: Hyperorthokeratosis and acanthosis with insignificant inflammation
- **Treatment**: Elimination of chronic trauma Cam K1,



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ;  
*Fitzpatrick's Dermatology in General Medicine*, 7th Edition: <http://www.accessmedicine.com>  
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# Oral Aphthae/Recurrent Aphthous Stomatitis

- **Presentation**: most common lesion of the oral mucosa - affect up to 25% of the general population
  - Tender lesions involving the non-keratinized mucosa (not bound to underlying periosteum)
  - Multiple, small, or ovoid ulcers, having yellow floors and are surrounded by erythematous haloes
  - 3 forms (3-10 mm in size): Minor. Major – when larger. Herpetiform – small 1-3 mm lesions grouped into a coalescing larger plaque, taking 1-4 weeks to resolve

# Oral Aphthae /Recurrent

## Aphthous Stomatitis

- **Pathogenesis** – true cause unknown, cell-mediated immune response, generation of T cells and production of TNF- $\alpha$ 
  - Triggers: hormonal changes, trauma, drugs, food hypersensitivity, nutritional deficiency, stress, & tobacco, Associated with: Behcet's, celiac, Inflammatory bowel disease, HIV
- **Histo**: pre-ulcerative lesion demonstrates subepithelial inflammatory mononuclear cells with abundant mast cells, connective tissue edema and lining of the margins with neutrophils.

# Oral Aphthae /Recurrent Aphthous Stomatitis

- **Treatment**

- NO permanent cure is available
- Topical analgesics
- Topical steroids
- Tetracycline mouth rinses
- Short course of systemic corticosteroids
- Systemics that reduce formation: Pentoxifylline, colchicine, dapsone and thalidomide

Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the Diagnosis and Treatment of Recurrent Aphthous Stomatitis for Dental Practitioners. *Journal of International Oral Health : JIOH*. 2015;7(5):74-80

Akintoye SO, Greenberg MS. Recurrent Aphthous Stomatitis. *Dental clinics of North America*. 2014;58(2):281-297.  
doi:10.1016/j.cden.2013.12.002





# Stomatitis Nicotina

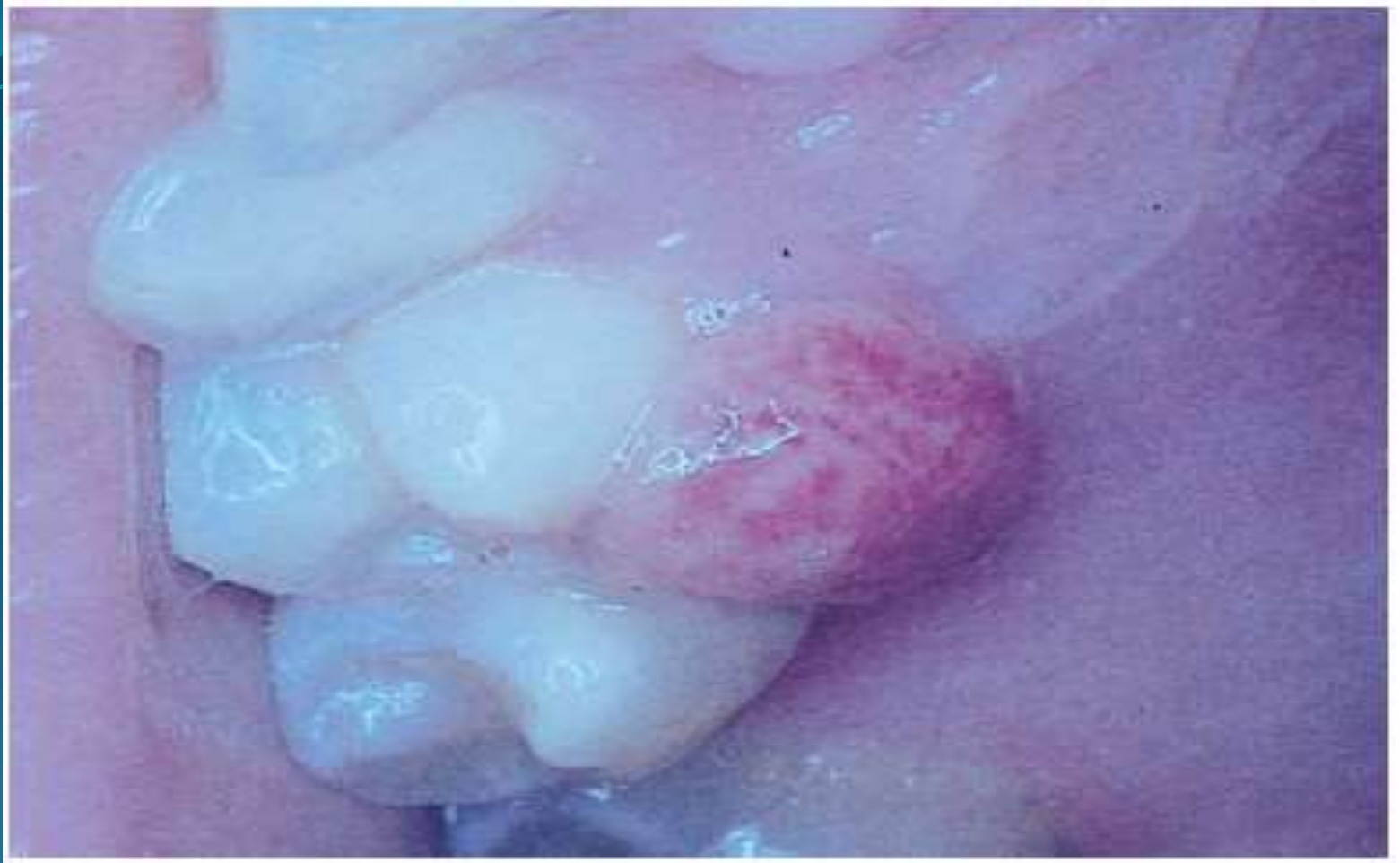
- **Presentation**: Umbilicated papules with central red depression affecting Hard palate/soft palate
- **Pathogenesis**: Inflamed palatal mucous salivary glands due to: Heavy smoking and Non-smokers who drink hot beverages
- **Histo**: Tissue biopsy not usually indicated
  - Acanthotic and hyperkeratotic
  - Mild to moderate chronic inflammation
- **Treatment**: Abstaining from tobacco and hot beverages

# Benign growths



# Mucocele

- **Presentation**: Soft, blue, translucent cyst (superficial) or mucosa-colored firm nodule (deep)
  - 2 to 10mm in diameter; Lower lip most commonly
  - Incision/compression releases sticky, straw colored or bluish fluid
- **Pathogenesis**: Obstruction or rupture of minor salivary glands; Trauma from biting
- **Histo**: One or more spaces filled with sialomucin; Lined by granulation tissue or a mixed infiltrate of fibroblasts, lymphocytes, and histiocytes
- **Treatment**: Excisional biopsy, Cryotherapy, Laser ablation



# Pyogenic granuloma

- **Presentation**: Red to reddish-purple, soft, nodular mass; Bleeds easily, grows rapidly
- **Pathogenesis**: Response to injury; Hormonal factors
- **Histo**: lobular capillary hemangioma; Lobules separated by connective tissue septae
- **Treatment**: Surgical excision; Pulsed dye or Nd:YAG laser; Cryosurgery





# Traumatic Ulcer

- **Presentation**: Painful ulceration
- **Pathogenesis**: accidentally biting oneself while talking, sleeping, or secondary to mastication
  - Also- Chemical, electrical, or thermal insults, may also be involved
- **Histo**: Surface ulceration covered by a fibrinopurulent membrane consisting of acute inflammatory cells intermixed with fibrin
  - Stratified squamous epithelium from the adjacent surface may be hyperplastic and exhibit areas of reactive squamous atypia
  - Ulcer bed is composed of a proliferation of granulation tissue with areas of edema and an infiltrate of acute and chronic inflammatory cells.
- DDx = SCC

# Traumatic Ulcer

- **Treatment**

- Removal of the irritants or cause
- Soft mouth guard
- Sedative mouth rinses
- Consumption of a soft, bland diet
- Warm sodium chloride rinses
- Topical corticosteroids
- Topical anesthetics

# Hereditary diseases



# White Sponge Nevus

- Benign, uncommon, AD disorder or sporadic; mutation in *KRT4* or *KRT13* gene, affecting non-keratinized stratified-squamous epithelia.
  - AKA familial white folded mucosal dysplasia, leukoderma exfoliativum mucosae oris, hereditary leukokeratosis
- **Presentation:** Onset in early childhood, 50% dx before age 20. White-to-gray, diffuse, painless, spongy folded plaques on the buccal mucosae > labial mucosae > tongue, floor of the mouth, and alveolar mucosae. Less frequently, the mucous membranes of the nose, esophagus, genitalia, and rectum are involved.
- **Pathogenesis:** attributed to an insertion, deletion, or substitution mutation in the helical domain of mucosal specific keratins, K4 and K13, causing an abnormal aggregation of tonofilaments and keratin filament instability.
- **Histo:** Parakeratosis, acanthosis with the formation of large, blunt rete ridges, spongiosis, and extensive vacuolation of suprabasal keratinocytes. Dyskeratotic cells exhibit dense peri-and paranuclear eosinophilic condensations, which correspond to tonofilament aggregates. Odland bodies are abundant within keratinocytes, but few are present in the intercellular spaces. This observation suggests a lack of acid phosphatase, which leads to retention rather than normal shedding of superficial cells.
- **Treatment:** No standard, reassurance only required. Generally, progression of the disorder stops at puberty and there is no malignant transformation. Oral abx can help.



# Osler-Weber Rendu Hereditary Hemorrhagic Telangiectasia

- **Presentation**: nosebleeds & telangiectasia, normal life span. ~1/3 pts: chronic anemia, w/ GIB increasing with age. Asymptomatic AV malformations occur in pulmonary (~50%), hepatic (~30%), cerebral (~10%) and spinal (~1%) circulations.
- **Pathogenesis**: AD mutations in endoglin (HHT1) or ACVRL1 (HHT2). Rarely due to mutations in Smad4, or other genes. Known disease genes involved in TGF- $\beta$  superfamily signaling. Marked intra-familial variation. Common AVM complications include stroke (ischemic and hemorrhagic) and brain abscess. Rarer HHT complications include DVT; symptomatic liver disease requiring liver transplantation; severe pulmonary HTN; pregnancy-related death; and spinovascular accidents.
- **Histo**: show focal dilatations of post capillary venules. Fully developed lesions have markedly dilated and convoluted venules extending through entire dermis with excessive layers of smooth muscle without elastic fibers, often connecting directly to dilated arterioles. Lymphocytes collect perivascularly.

# Osler-Weber Rendu-HHT

- **Treatment**: repair Nasal telangectasia 90%
  - Sx: Nosebleeds & Iron deficiency anemia, Nasal humidification; packing in emergencies. ENT: laser; surgery; embolisation; Systemic: estrogen–progesterone, antifibrinolytics
  - Repair Mucocutaneous telangiectasia – 80%; repair Gastrointestinal telangiectasia – 20%; repair Pulmonary AVMs - 50%
  - Tx: Laser or other ablation therapies
  - Cerebral AVMs- 10%; Hepatic AVMs- 30%; Spinal AVMs <1%
  - Tx: Iron +/- transfusions for anemia in all cases.





# MEN2B: Multiple Endocrine Neoplasia

- **Presentation:** mucosal neuromas of the lips, tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the GI tract, and a 'marfanoid' habitus. Medullary thyroid carcinoma (MTC) typically occurs in early childhood in MEN 2B. \*\*High risk for development of MTC, increased risk for pheochromocytoma,
- **Pathogenesis/Diagnosis:** AD. Molecular genetic testing to identify a heterozygous germline RET pathogenic variant is indicated in all individuals with a diagnosis of primary C-cell hyperplasia or MTC or a clinical diagnosis of MEN 2. Identification of a heterozygous germline RET pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.
- **Histo:** Unencapsulated masses of convoluted nerve fibers surrounded by a thickened perineurium. = plexiform neuromas.
- **Treatment:** thyroidectomy and lymph node dissection. External beam radiation therapy or intensity-modulated radiation therapy can be considered for advanced regional disease. Kinase inhibitors may be used in metastatic MTC. >>Pheos can be removed by adrenalectomy. Primary hyperparathyroidism is treated by parathyroidectomy, or more rarely, medications to reduce parathyroid hormone secretion. ALL PTS NEED YEARLY HORMONE MONITORING.
  - **Prevention of primary manifestations:** Prophylactic thyroidectomy for individuals with an identified germline RET pathogenic variant.

Marquard J, Eng C. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2015 Jun 25]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1257/>

Multiple idiopathic mucosal neuromas: A minor form of multiple endocrine neoplasia type 2B or a new entity? Pujol, Ramon M. et al. Journal of the American Academy of Dermatology, Volume 37, Issue 2, 349-352.



# LEOPARD Syndrome

- **Presentation:** Lentigines, EKG defects, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth , Deafness (sensorineural).
  - Facial dysmorphism : ocular hypertelorism, palpebral ptosis and low-set ears. Stature is usually below the 25%. Cardiac defects hypertrophic cardiomyopathy - left ventricle. The lentigines may be congenital, although more frequently manifest by the age of 4–5 years and increase throughout puberty. Additional common features are café-au-lait spots (CLS), chest anomalies, cryptorchidism, delayed puberty, hypotonia, mild developmental delay, sensorineural deafness and learning difficulties.

# LEOPARD Syndrome

- **Pathogenesis**: Missense mutations: exons 7, 12, or 13 of the PTPN11 gene in 90% of the cases. Others can be RAF 1 or de novo mutations. Mutations in PTPN11 affect RAS–MAPK pathway activity by up-regulating SHP-2 activation through impairing the switch between its active and inactive conformation without altering SHP-2's catalytic capability.
- **Histo**: Lentigines have increased number of melanocytes per unit skin and prominent rete ridges.
- **Treatment**: LS should be suspected in fetuses with severe cardiac hypertrophy (risk of sudden cardiac death) and prenatal DNA test may be performed.

Gorlin, R. J., Anderson, R. C. and Moller, J. H. (1971), The leopard (multiple lentigines) syndrome revisited. *The Laryngoscope*, 81: 1674–1681.

Delayed primary diagnosis of LEOPARD syndrome type 1. Staub, Janina et al.

*Journal of the American Academy of Dermatology*, Volume 68, Issue 2, e58 - e60

# Systemic Disease



# Hypertrophic gingivitis

- **Presentation**: increased size of the gingiva
- **Pathogenesis**: Inflammatory enlargement (from poor oral hygiene); Drug induced enlargement (anticonvulsants, CCB,CsA); Enlargement associated w/ systemic diseases or conditions (preg,puberty,vit c def,pyogenic granuloma); Neoplastic enlargement (carcinoma or melanoma); False enlargement (underlying bony or dental tissue lesion).
- **Histo**: Acanthosis, parakeratosis w/ pseudoepitheliomatous proliferation. Highly vascular connective tissue w/ focal accumulation of inflammatory cells, primarily plasma cells. IHC: increase in the number of Langerhans cells within the epithelium and adjacent to inflamed sites.
- **Treatment**: improved oral hygiene; change the offending drug, and/or correct/associated disease/malignancy, if applicable.





Figure 2 – Irregularly shaped bullae are seen on both the hard and soft palate of a patient with pemphigus vulgaris. Pain is the predominant symptom of this potentially fatal disorder.

# Pemphigus Vulgaris

- **Presentation – PV:** delicate, superficial labial & buccal mucosal ulcers. Desquamative gingivitis occurs (can also be seen in oral LP and mucous membrane pemphigoid)
  - Oropharynx, esophagus can be involved. 50% pts will have skin PV.
  - Nail dystrophy, paronychia, and subungual hematomas
- **Paraneoplastic pemphigus (PNP)** similar exam findings to PV and lichenoid, targetoid and tense blisters.
  - PNP - painful, progressive stomatitis of the tongue. In addition, the presence of blisters and targetoid lesions on the palms and soles can help differentiate PNP from PV. A biopsy with direct immunofluorescence (DIF) and a complete physical exam can further help differentiate PNP from PV.
- **Pathogenesis: PV:** IgG autoantibodies against desmoglein 1 → acantholysis. Mucocutaneous PV have detectable autoantibodies directed against Dsg-1 and Dsg-3 whereas patients with *only* mucosal disease have antibodies targeted against only Dsg-3. The triggering event leading to antibody formation is unknown.
  - Pts w/**PNP** also have autoantibodies against Dsg-1 and Dsg-3. In addition, PNP has antibodies targeted against proteins in the plakin family (plectin, desmoplakin I, desmoplakin II, bullous pemphigoid antigen I, envoplakin, and periplakin). These plakin proteins are also involved in cell-cell adhesion of keratinocytes.

# Pemphigus Vulgaris

- **Histo:** intraepithelial blister with few inflammatory cells (eos), some acantholytic cells and tombstoning at basal layer; w/ moderate perivascular chronic inflammation. DIF: intercellular deposition of IgG and C3 in a “chicken-wire” lattice pattern.
- **PNP** - variable presentation – similar to PV, LP, and EM; an intraepithelial blister with suprabasal acantholysis, interface dermatitis, dyskeratotic keratinocytes, and lymphocyte exocytosis. Spongiosis, chronic perivascular and lichenoid infiltrates and pigment incontinence can also be seen. DIF shows IgG deposition in all layers of the epidermis and C3 in the lower epidermis and basement membrane. In contrast to PV, intercellular staining is often focal and faint.

# Pemphigus Vulgaris

- **Treatment PV:** Topicals: High-potency corticosteroids (rinses, gels, pastes), Tacrolimus ointment 0.1%. First line txs: Corticosteroids 1 mg/kg/day w/ clinical remission in 4–12 weeks,
  - Rituximab: 4 weekly infusions at 375 mg/m<sup>2</sup> of BSA (oncology dosing) or 1000 mg × 2 separated by 2 weeks (rheumatology dosing)
  - Others: IVIG (sometimes combined with rituximab), Azathioprine, Mycophenolate mofetil, Cyclophosphamide, MTX, gold, CsA, plasmapheresis, extracorporeal photochemotherapy, anti-TNF- $\alpha$ , thalidomide.
- **Treatment PNP:** Prednisone (0.5–1 mg/kg), CsA(5 mg/kg), sometimes combined w/ prednisone, Cyclophosphamide (2mg/kg), sometimes combined w/prednisone and CsA, Immunoablative cyclophosphamide without stem cell rescue, Immunoapheresis, IVIG, Rituximab, Alemtuzumab



# Pyostomatitis Vegetans

- **Presentation:** chronic mucocutaneous ulcerative disorder associated with IBD and consisting of multiple miliary white or yellow pustules with an erythematous and edematous mucosal base. The pustules can rupture and coalesce to form linear or “snail-track” ulcers. The labial gingiva, labial, and buccal mucosa are most frequently involved.
  - Prevalent between 20 and 59 years, M > F (2:1-3:1).
  - Is oral equivalent of pyodermitis vegetans on the skin.
  - Intestinal involvement usually predates its onset in IBD. Pts present w/ fever, enlarged and tender submandibular lymph nodes, and pain. Eosinophilia is seen in 90% of cases.
- **Pathogenesis:** unknown, a marker of disease severity in UC, associated with IBD (primarily UC)
  - **DDx:** PV, BP, EBA, bullous drug eruptions, herpetic infection, Behçet’s disease, and EM, HSV
- **Histo:** intra-epithelial and/or sub-epithelial micro-abscesses w/ neutrophils and eosinophils w/ hyperkeratosis, acanthosis, and acantholysis. DIF is negative for deposits of IgA, IgG and C3 and this result is helpful in distinguishing it from pemphigus vulgaris.

# Pyostomatitis Vegetans

- **Treatment:** tx underlying IBD.
  - Topical steroids & antiseptic mouthwashes are sometimes effective.
  - Systemic steroids = treatment of choice.
  - Azathioprine and sulfamethoxypyridazine can be used in parallel with steroids as sparing agents. Dapsone is another option, but should be used as a second line agent, especially in relapsing cases. CsA has been successfully used. Injections of infliximab followed by maintenance therapy w/ Mtx have been also effective, especially when this disease is associated with Crohn's. Humira has also proven effective in inducing remission of both oral and GI manifestations. Surgical colectomy produces promising results in this disease when associated with ulcerative colitis.

The End