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Medical Derm Society
Oral Manifestations of Autoimmune and Inflammatory Disease

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- I have no financial disclosures or conflict of interests

- I will discuss off label indications of medications

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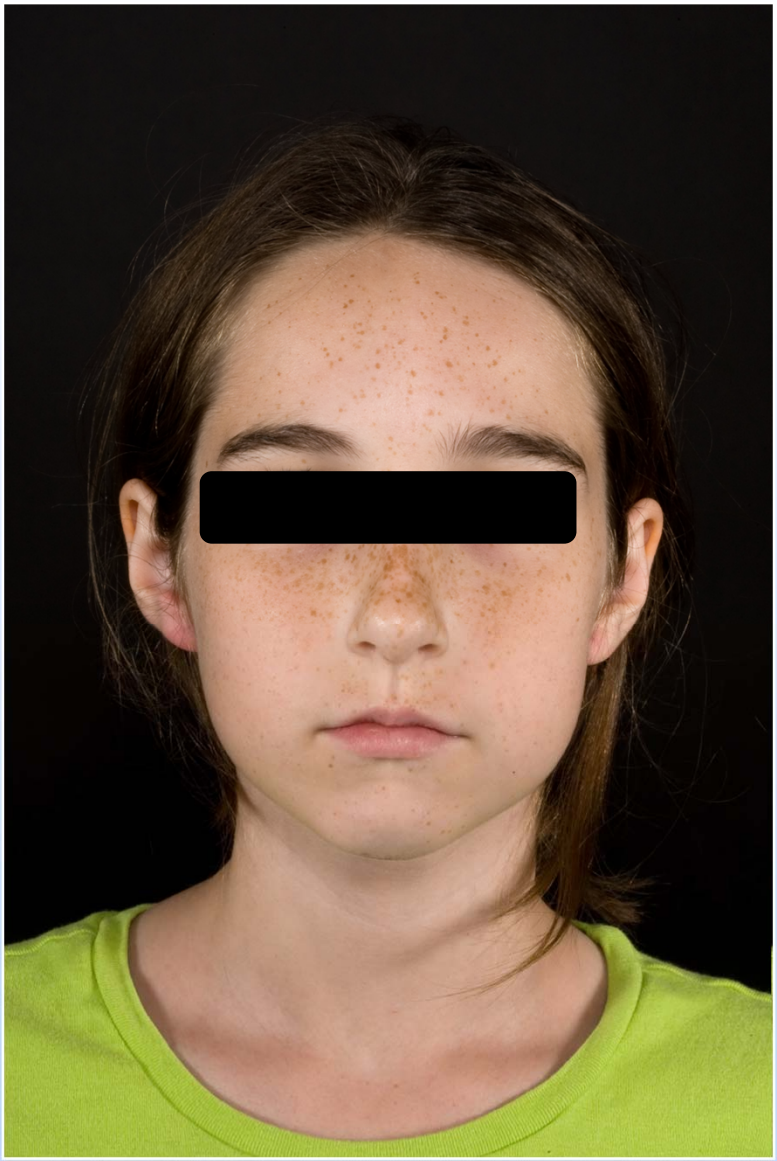
Case #1: 10 yo female

- 3 weeks hx of painless left sided facial swelling
- Negative ROS
- Normal labs (CBC, ESR, chem)



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The best diagnostic test is:

- Fine needle aspirate of swelling
- MRI of face and parotid gland
- Colonoscopy
- Bone scan
- Panoramic dental X-ray

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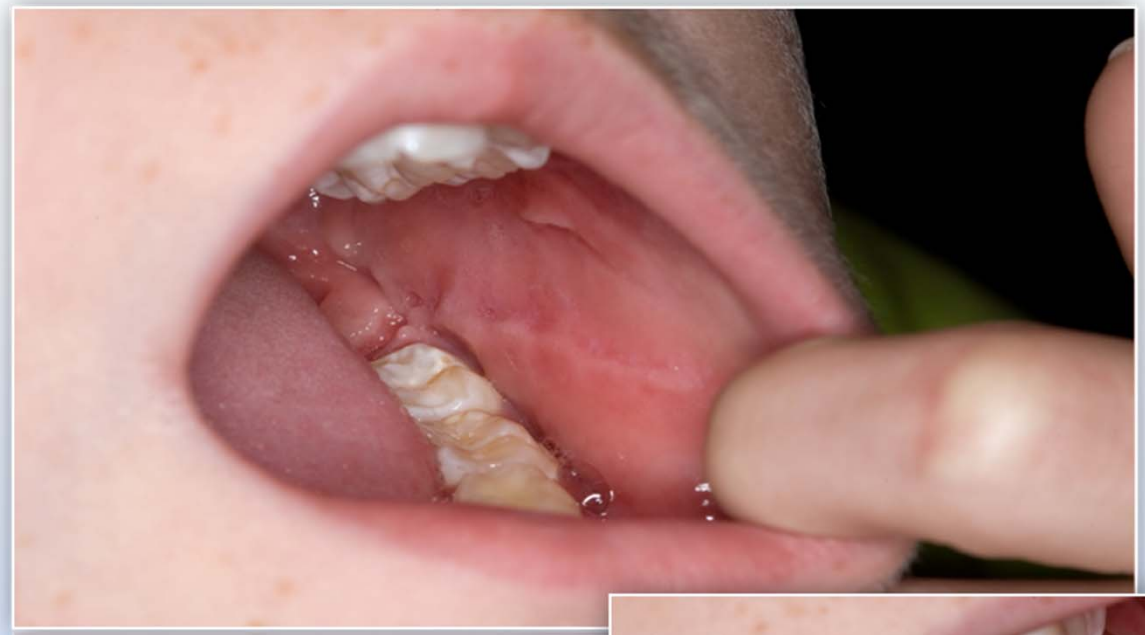

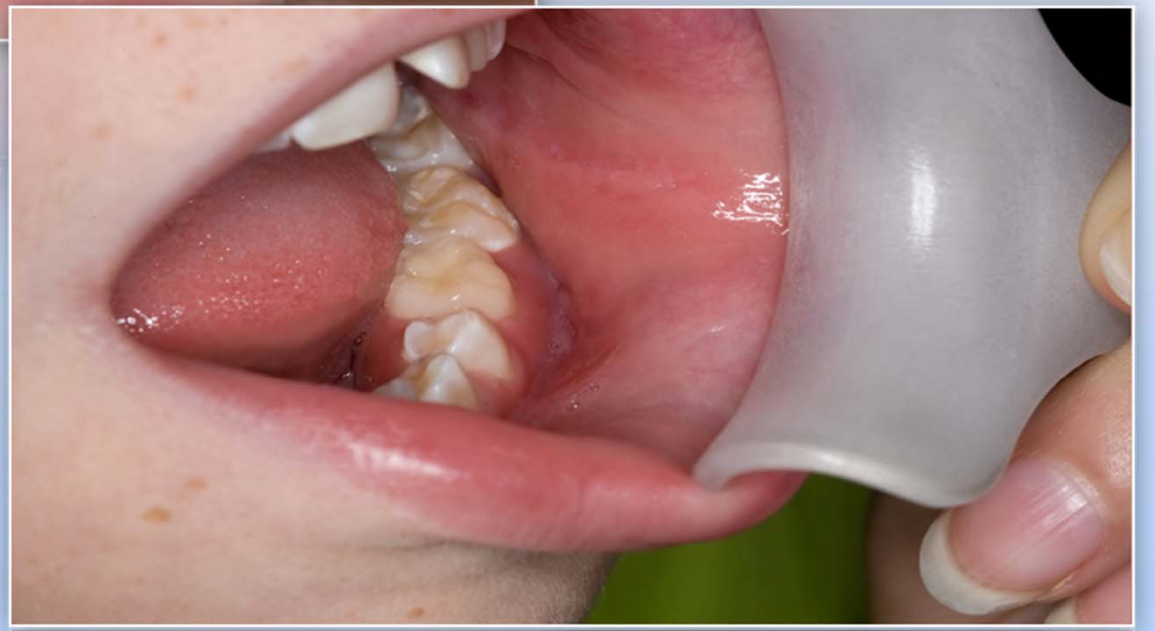

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- MR enterography normal
- Upper endoscopy and colonoscopy - GRANULOMAS

- Dx: Crohns disease
- Commenced treatment with Azathioprine
- Complete remission 1 yr later

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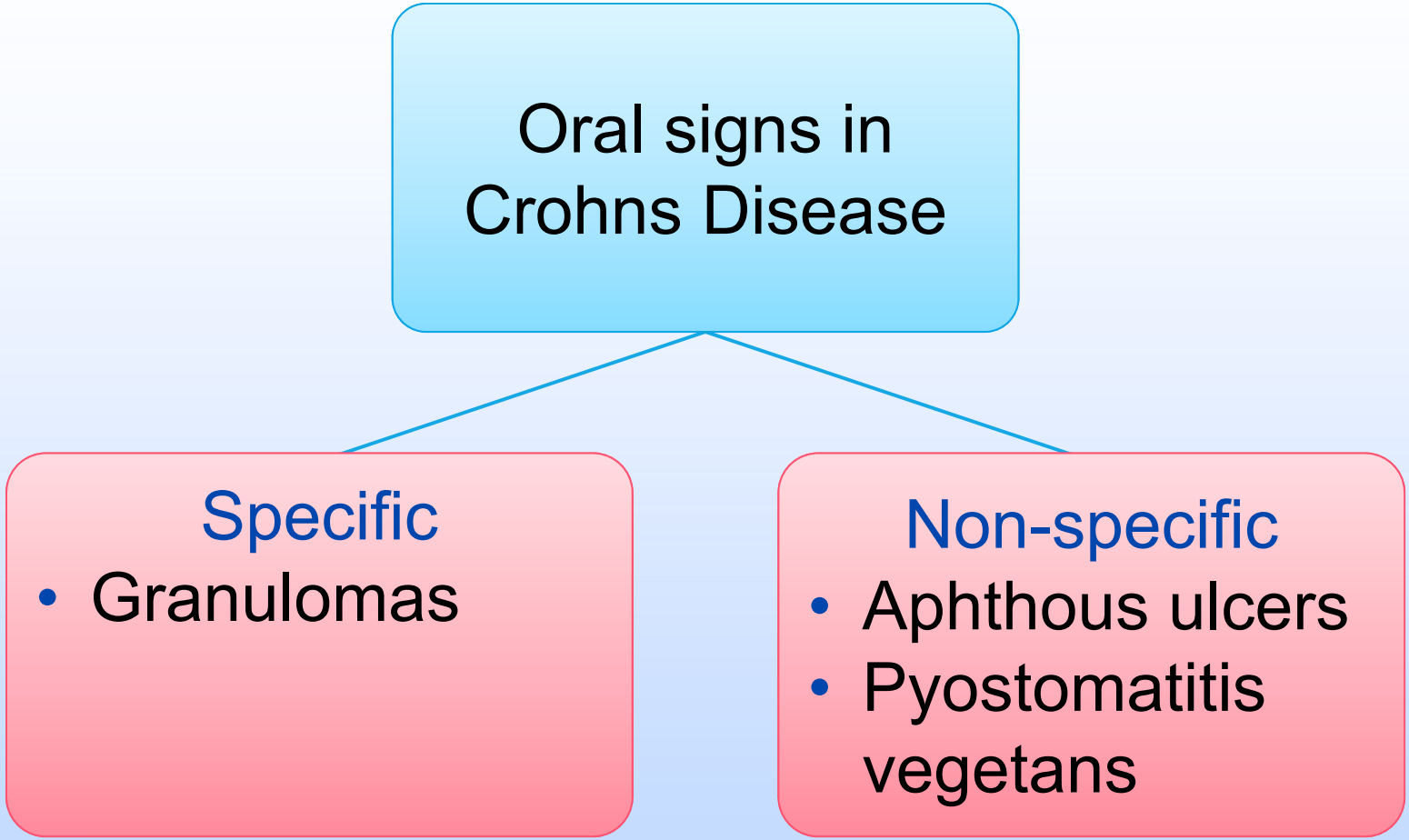

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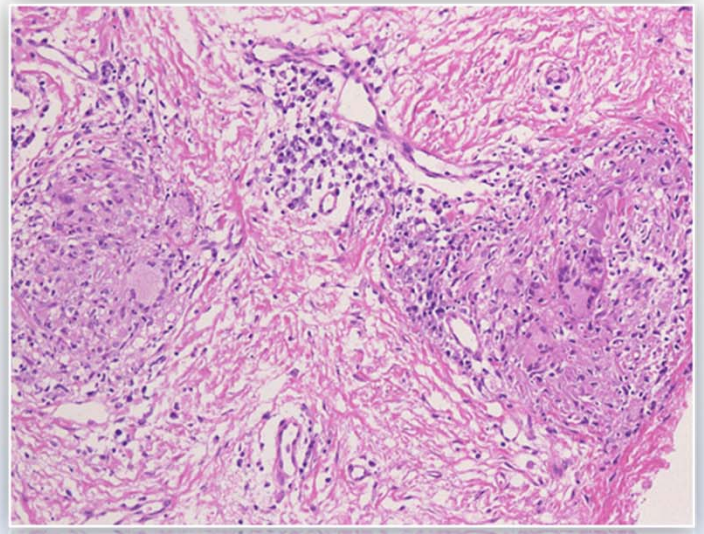
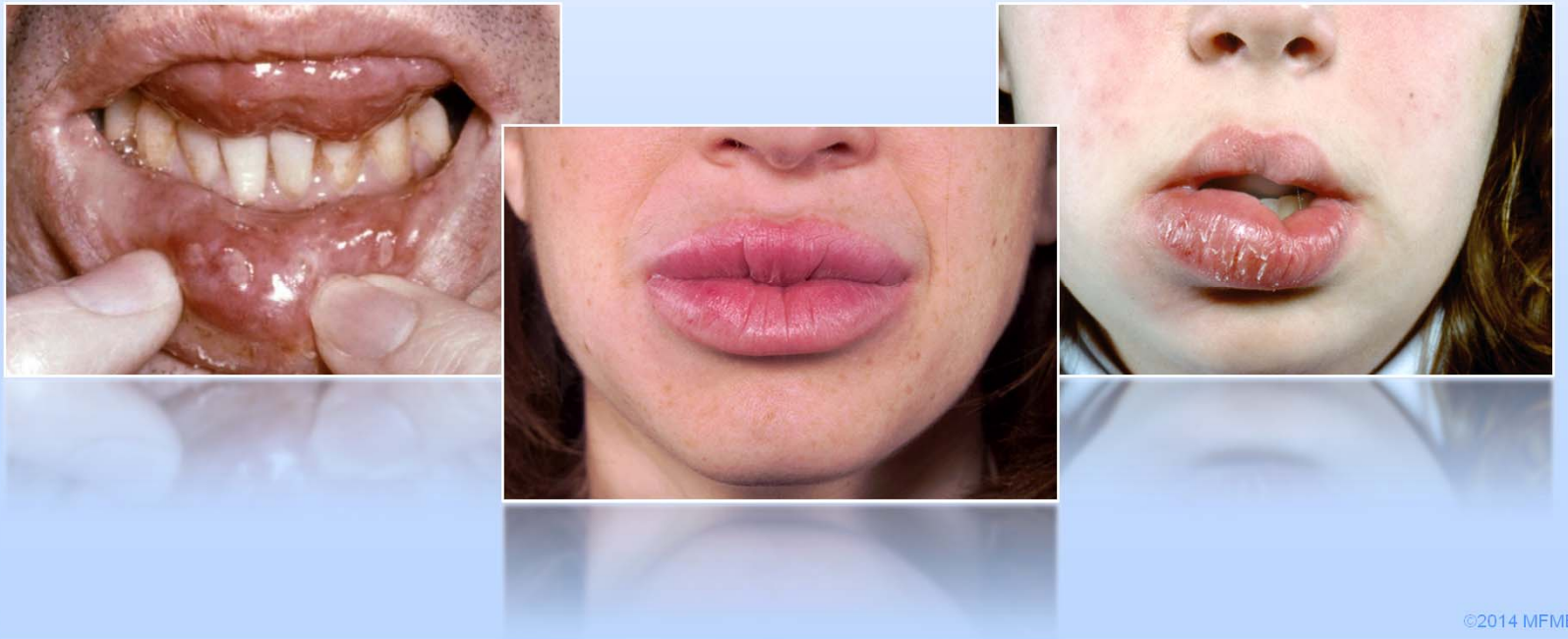
Oral Features

- Lips
  - Labial enlargement



Sub mucosal nodules of lips (granulomas)



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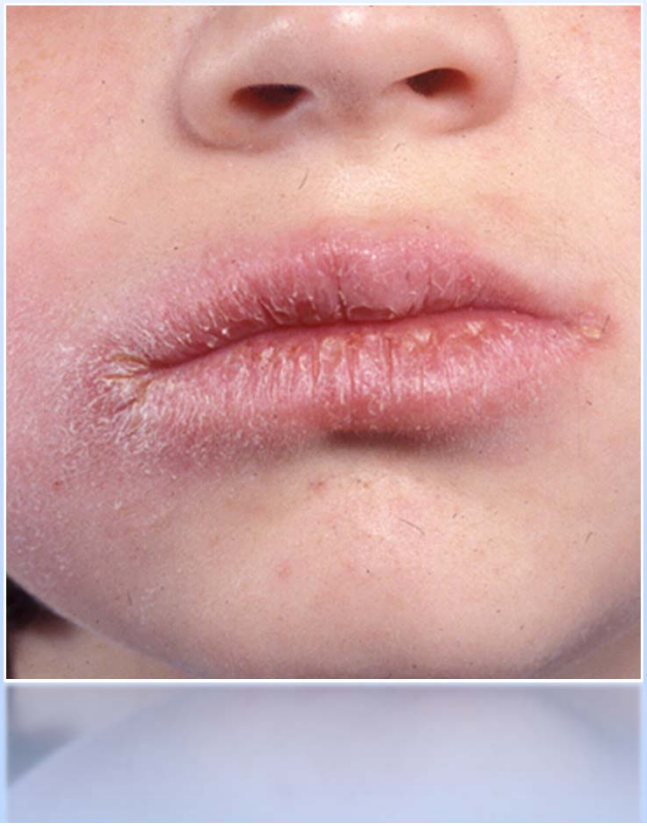
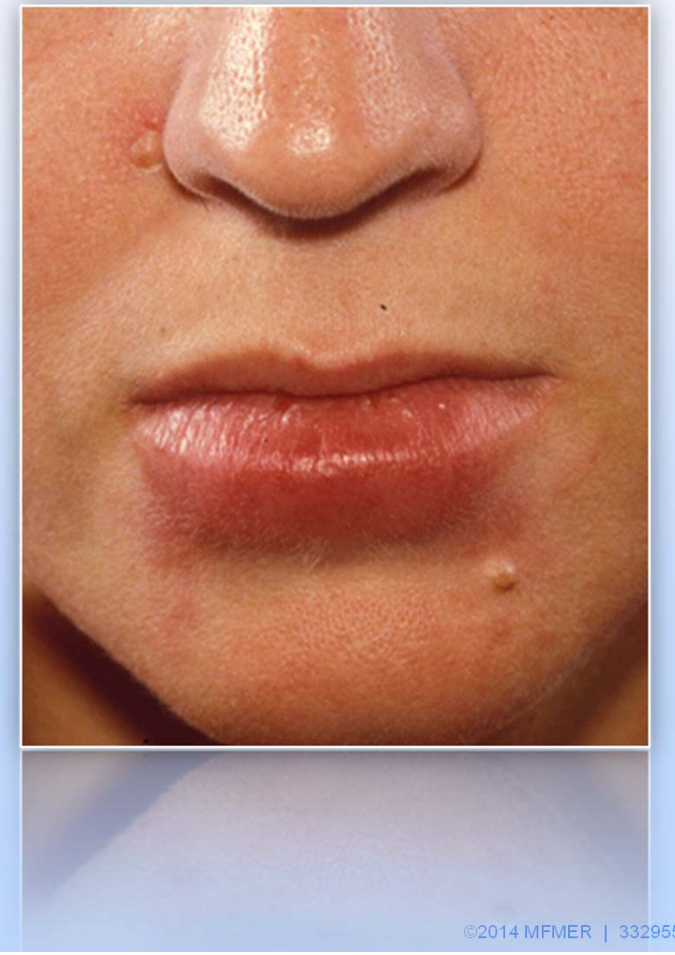
Lips

- Labial mucosa may be erythematous, granular
- Perioral skin dry/exfoliative





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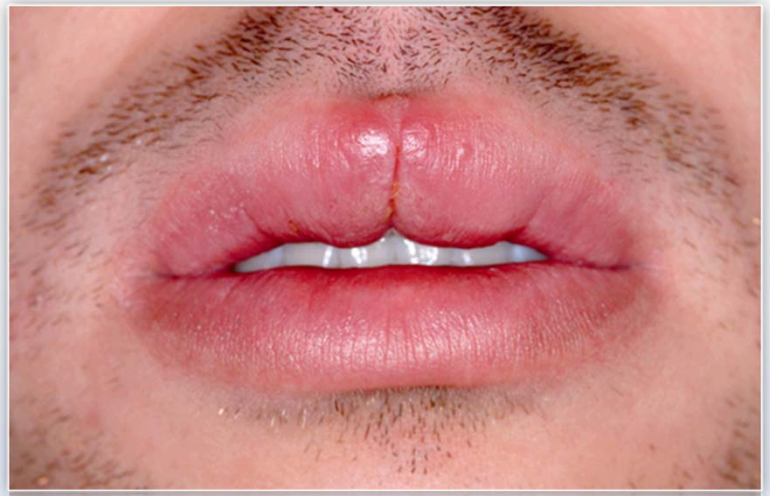
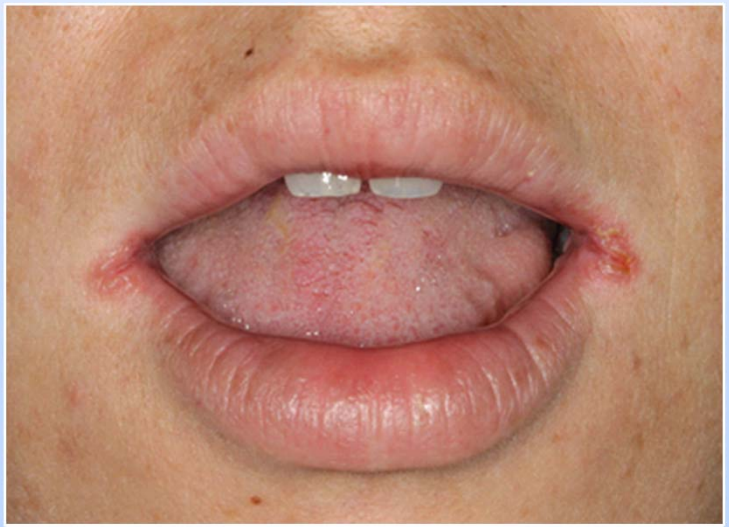
Lips

- Midline fissuring (median cheilitis)



- Fissuring at angles of mouth (angular cheilitis)



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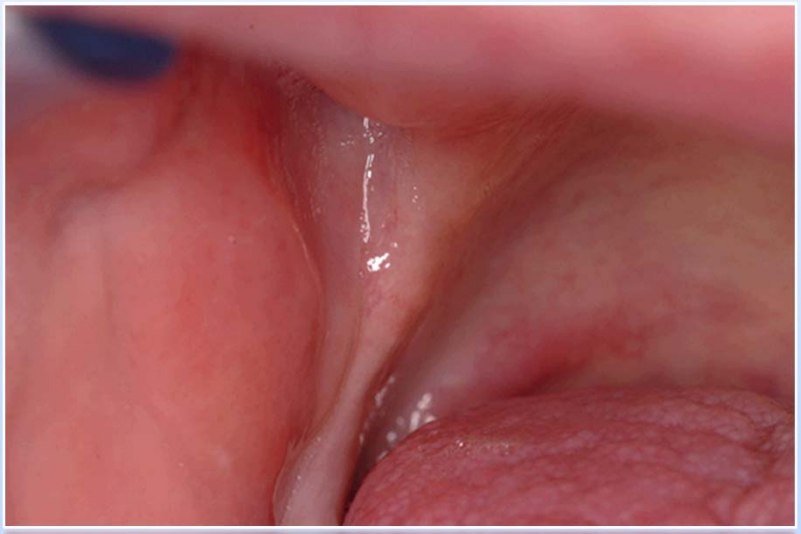
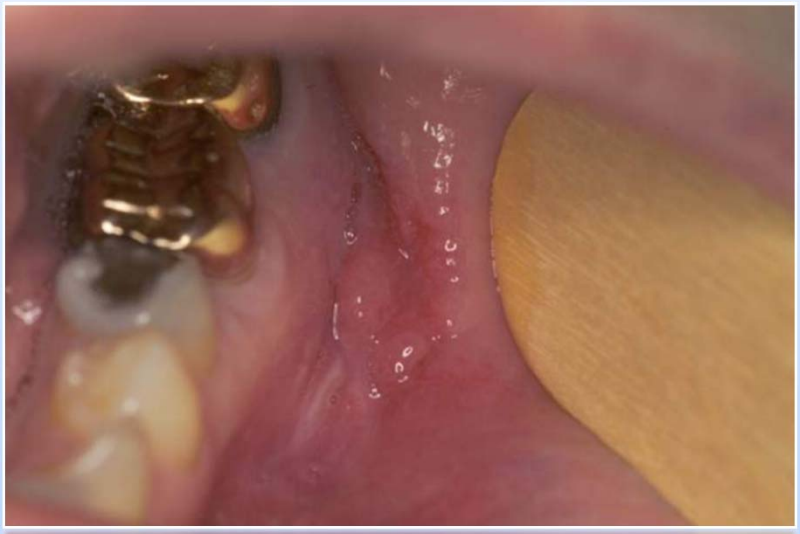
Intraoral Mucosa

Mucosal swelling

- Rugae of intra-oral mucosa





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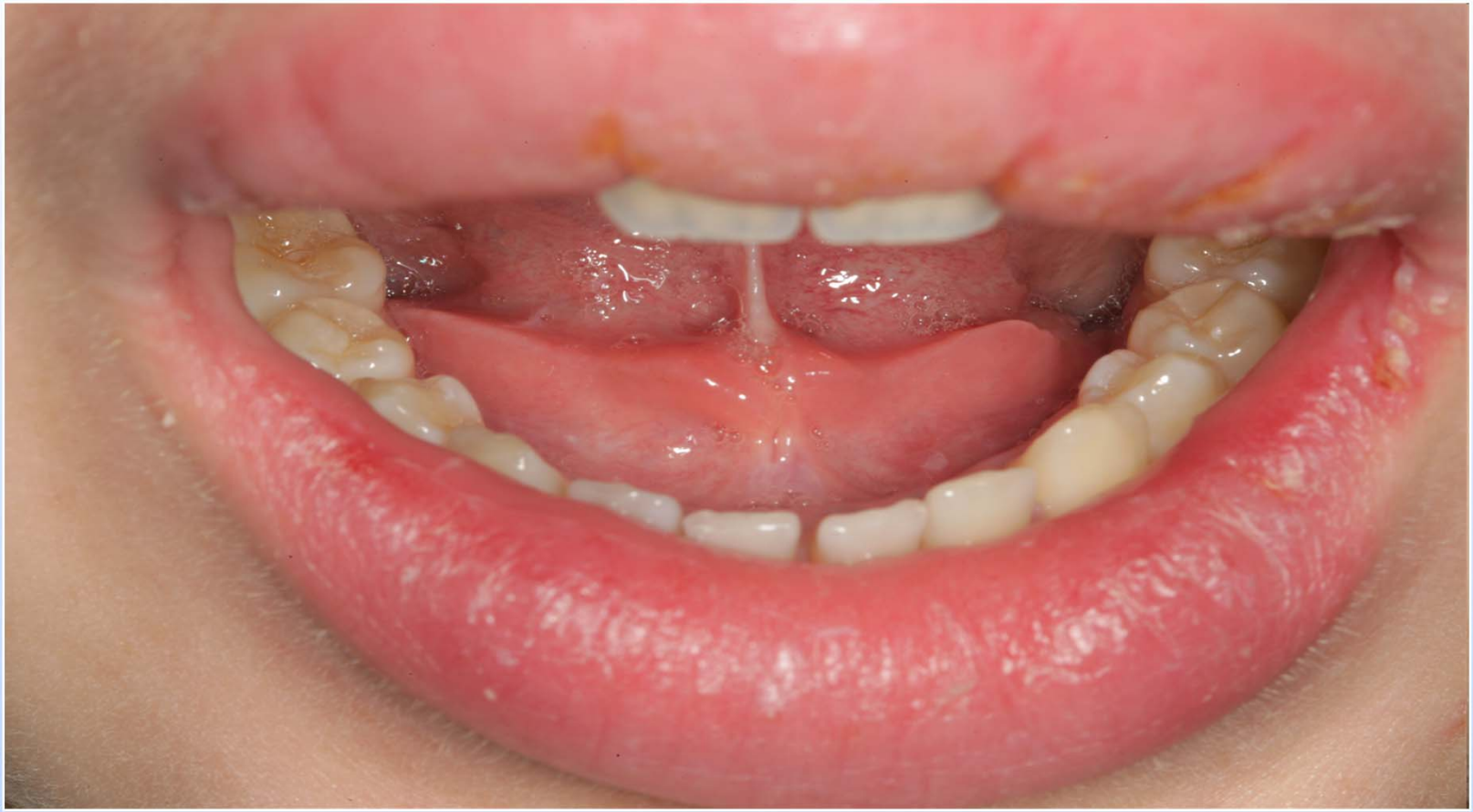
Staghorn Sign



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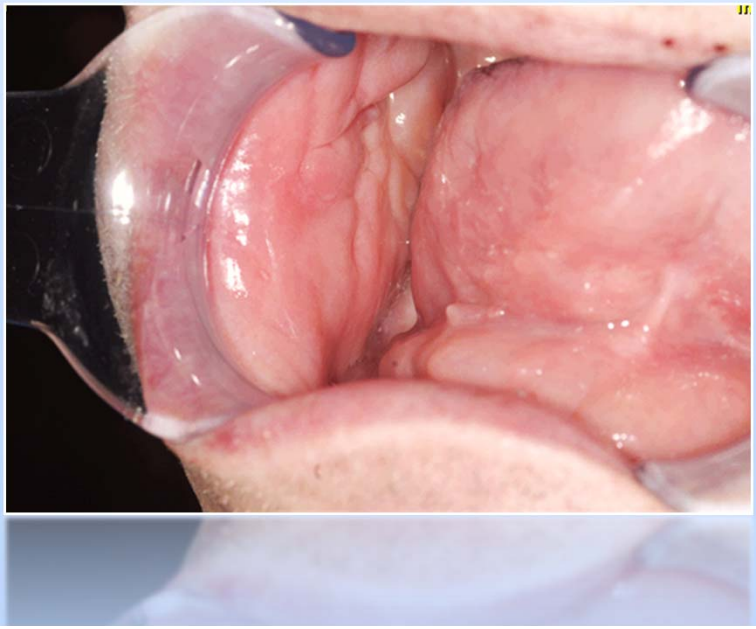
Intraoral Mucosa

Cobblestoning

- Buccal mucosae swollen – distinct folds
- Similar to intestinal mucosa



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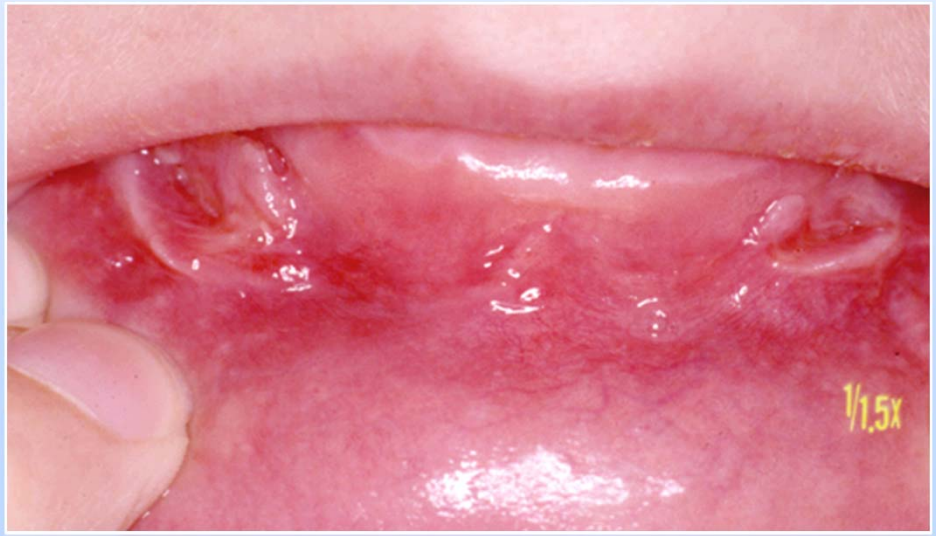
Intraoral Mucosa

Ulcers

- Most common – chronic, deep in buccal or labial vestibule with raised borders



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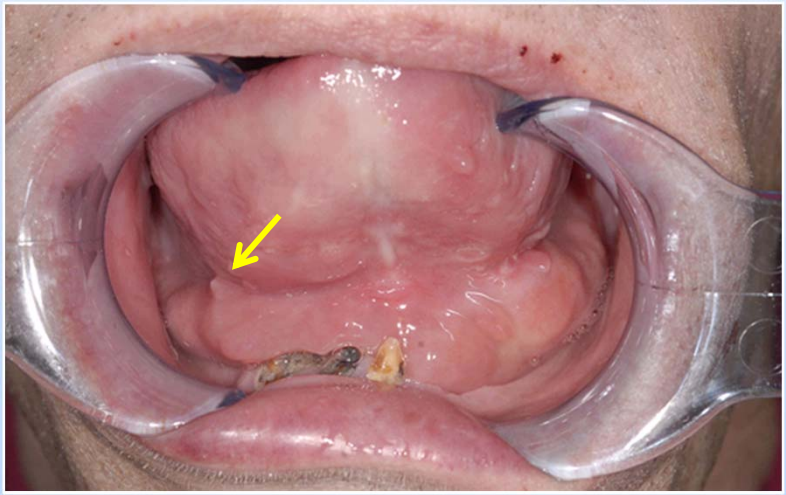
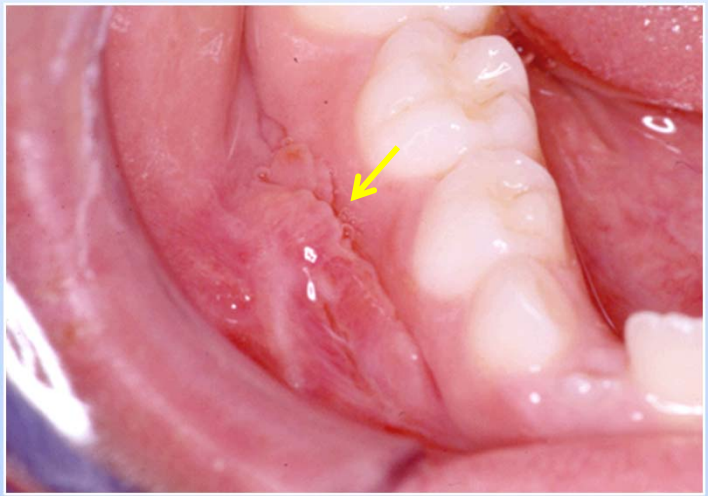
Intraoral Mucosa

Mucosal Tags

- Arise in vestibule or retromolar region
- Pink / red tags
- Similar to raised borders of chronic ulcers





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Gingivae

- Painless enlargement (localized or generalized)
- Granular appearance, salmon pink / red

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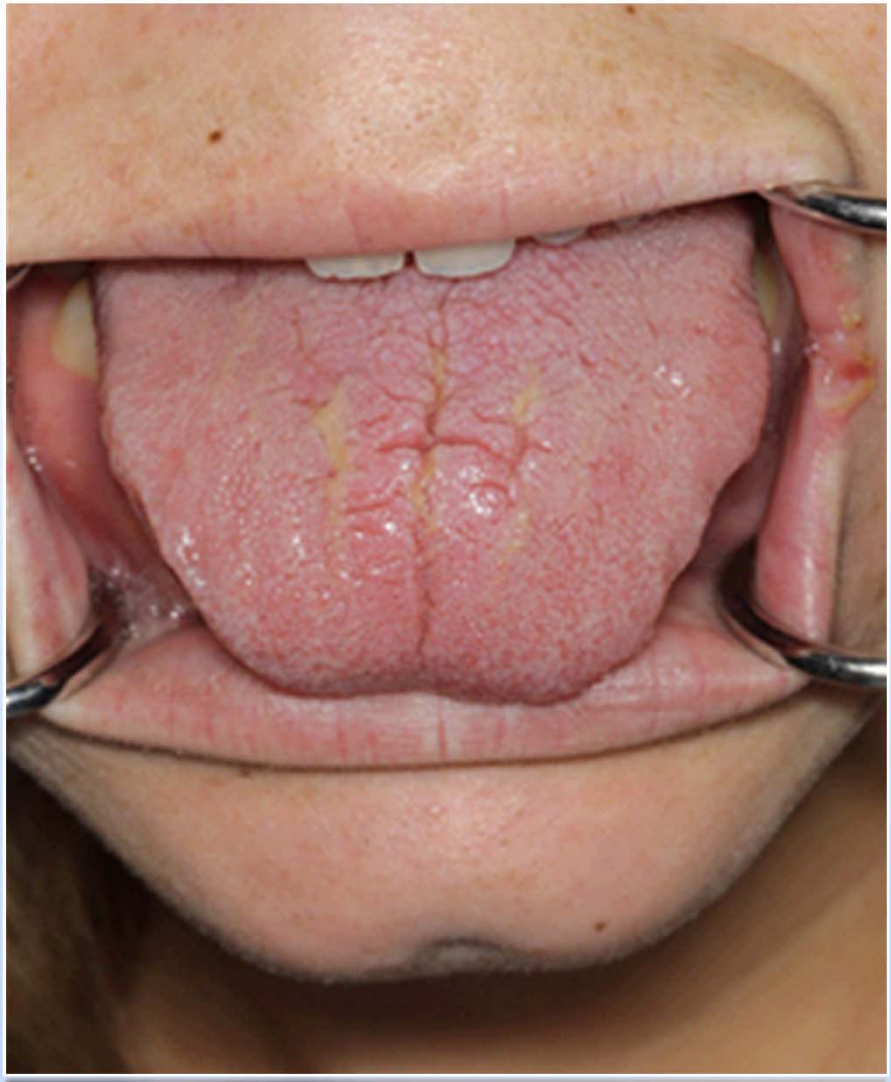
Tongue

- Fissuring



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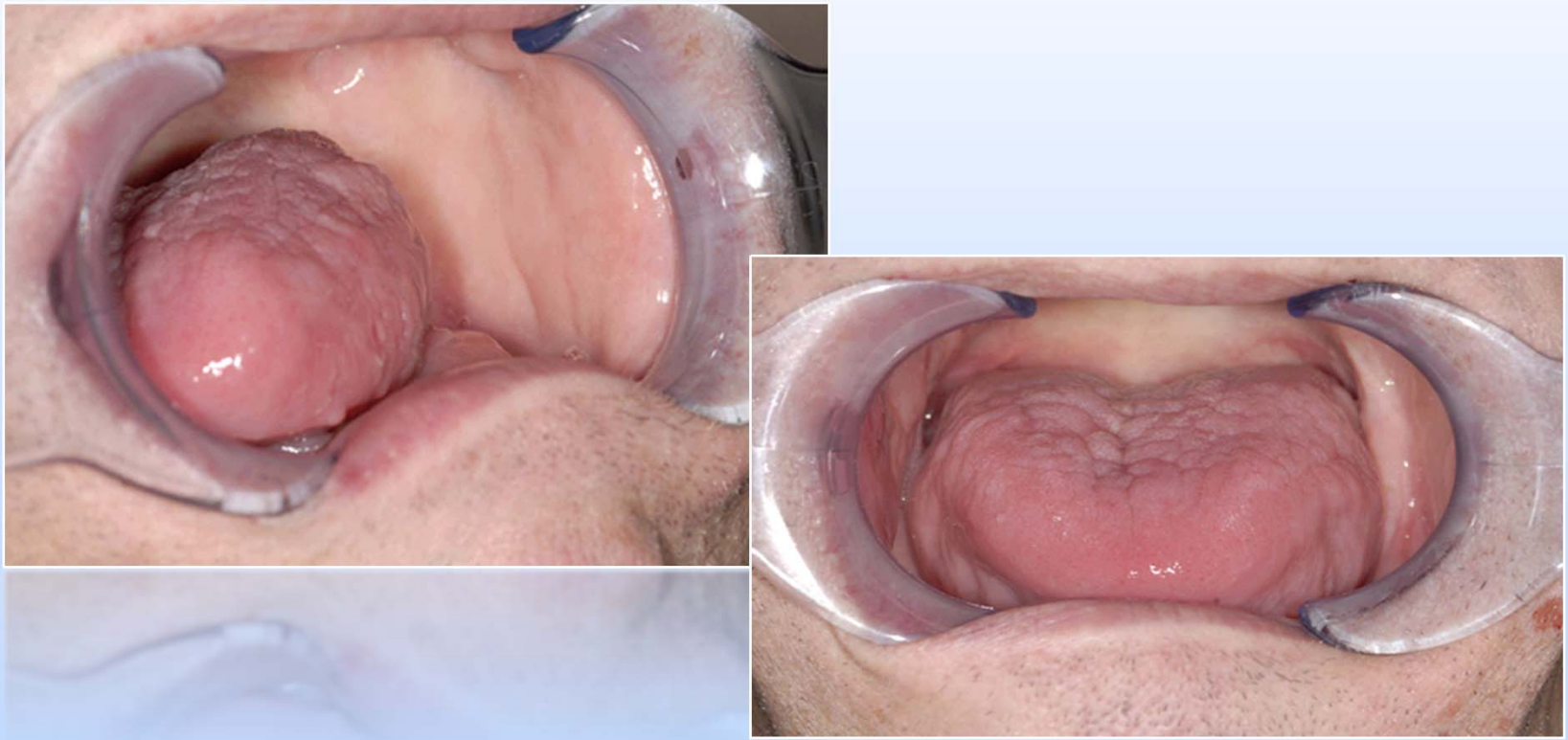
Tongue

- Swelling



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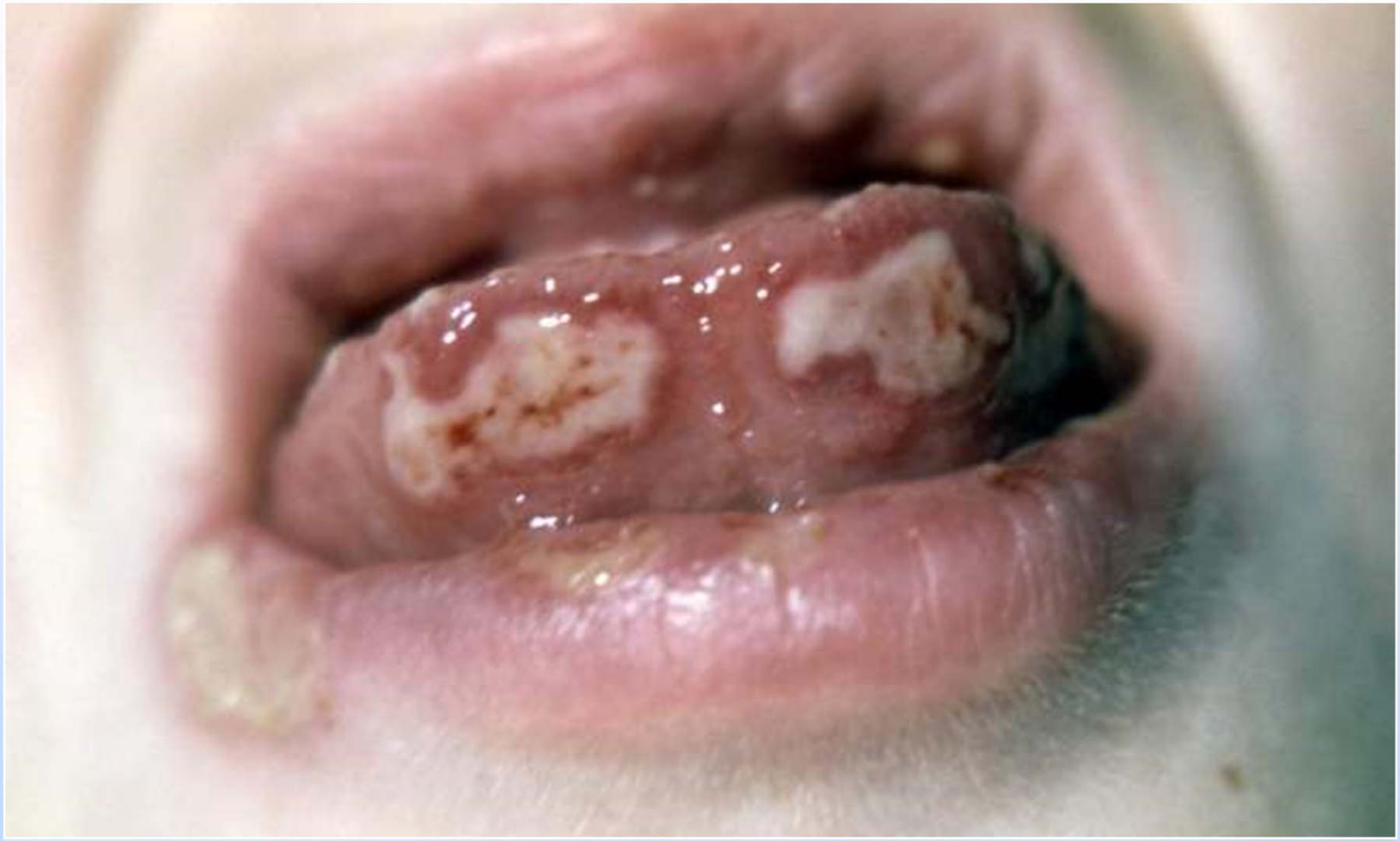
Non-specific manifestations (reactive)



Major Aphthous Ulcers with Crohns Disease

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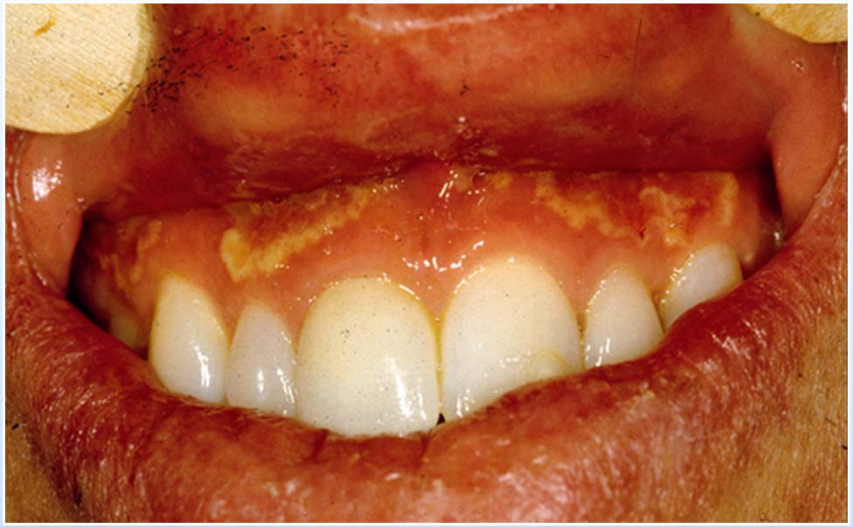
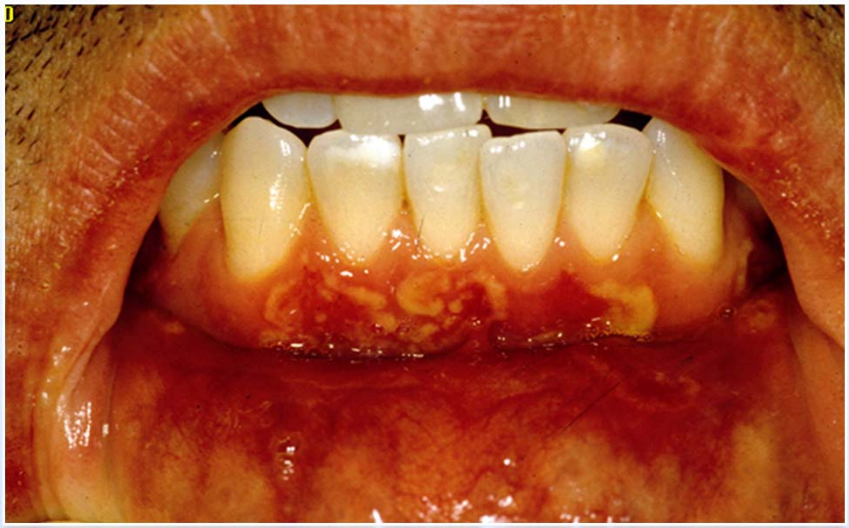
Pyostomatitis Vegetans





- Akin to pyoderma gangrenosum
- Rare, more common Ulcerative Colitis

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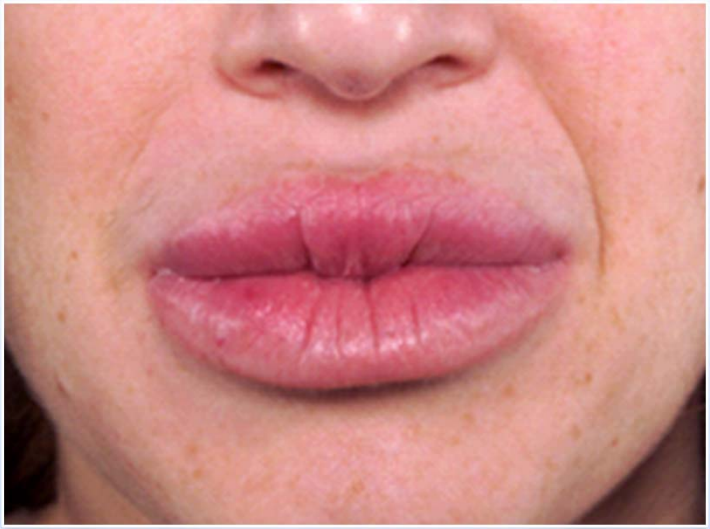
Orofacial Granulomatosis

- Persistent swelling – characteristically lips
- Granulomas + lymphedema
- Etiology
  - Idiopathic
  - Sarcoid
  - Infection (mycobacterial)
  - Allergy (dental mental/food)
  - IBD



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Southeast England Study*

- 207 OFG pt
  - 22% had coexisting intestinal CD
- Majority neither had, nor evolved to CD
- Progression to CD more likely if OFG onset in childhood (<16 yr)

*Campbell et al: Inflamm Bowel Dis, 2011

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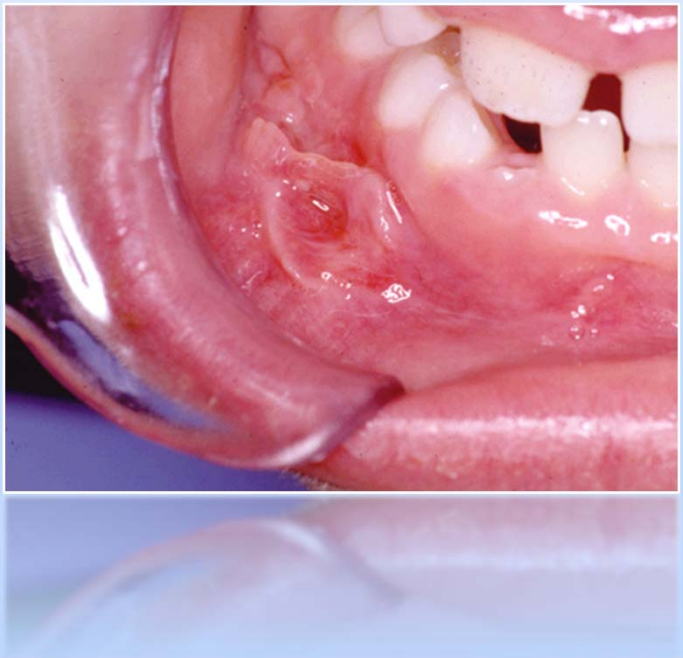
Clinical Markers

- Ulceration
- Less lip, more buccal and sulcal involvement
- “Posterior” pattern of disease with CD vs “anterior” pattern without CD



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Biomarkers

- Abnormal CBC, low Hb, raised CRP
- Positive Sacromyces cerevisiae Ab (ASCA)
- OFG with GI abnormalities - don't always evolve to classic CD – "OFG with gut involvement"

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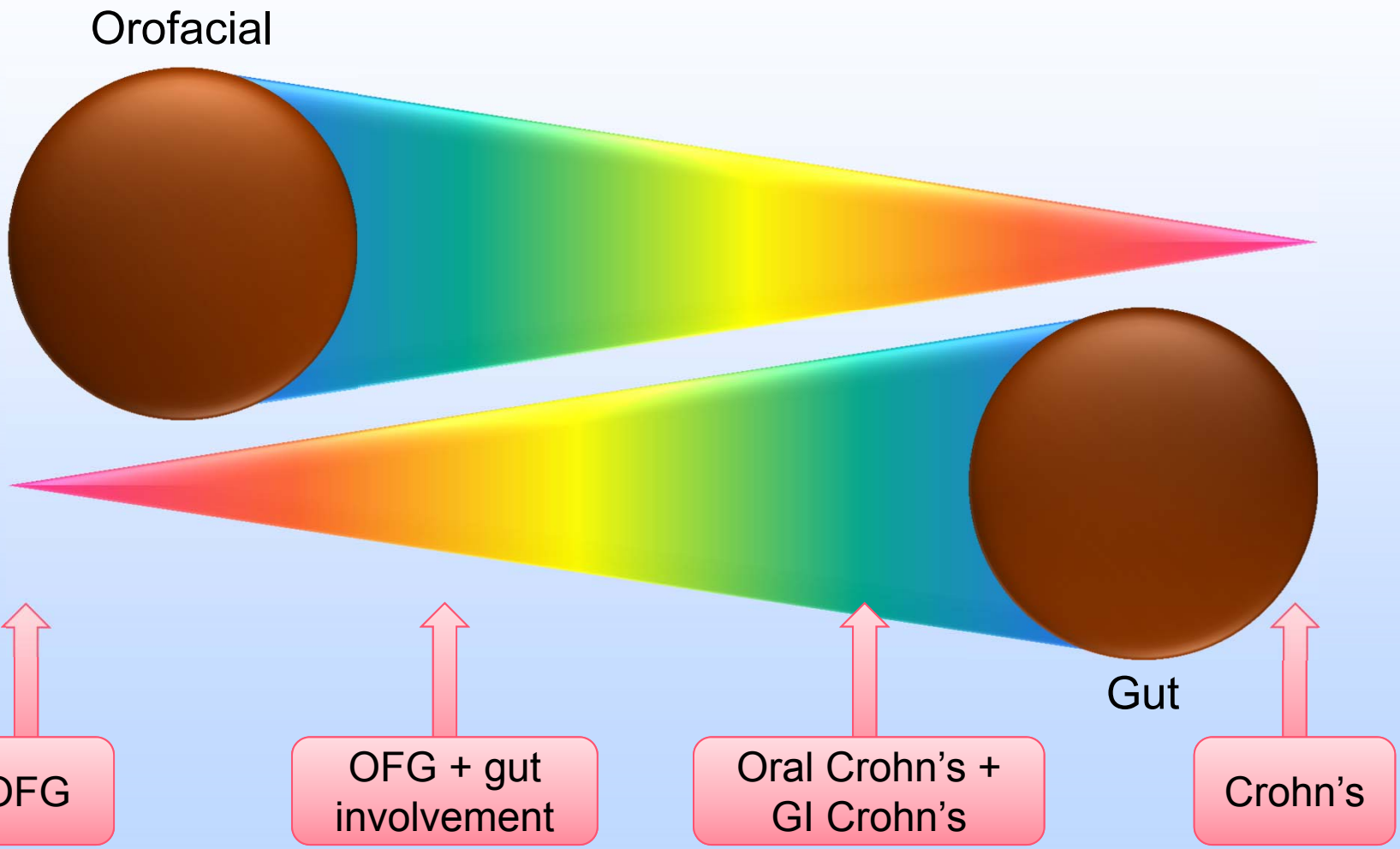
Spectrum



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Evaluation

- Should all pt with OFG have GI w/u?
- Referral to GI may yield microscopic disease in asymptomatic patients
- Warranted in young pt / + family history
- At minimum, long-term follow-up in younger pt

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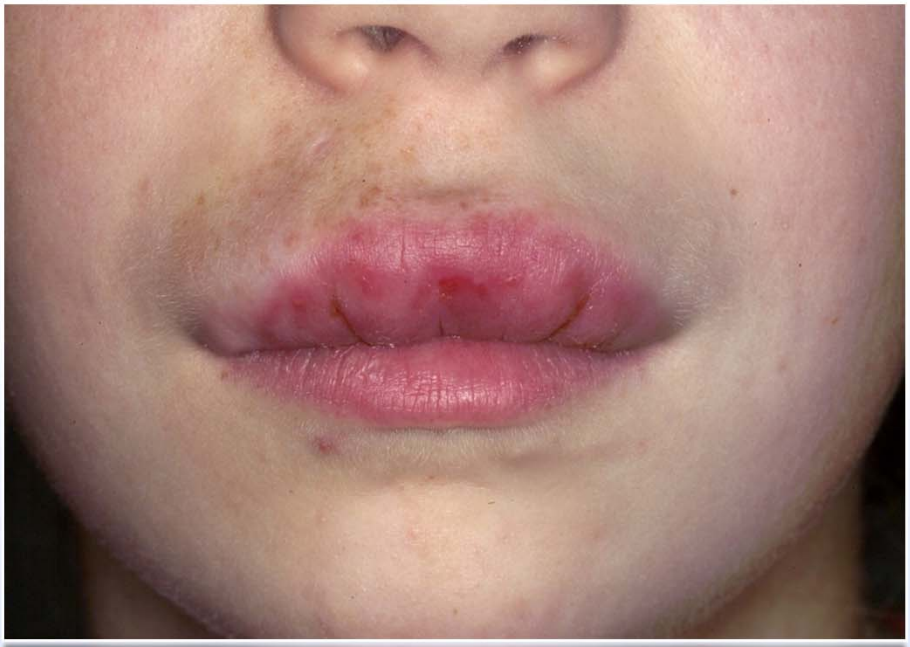

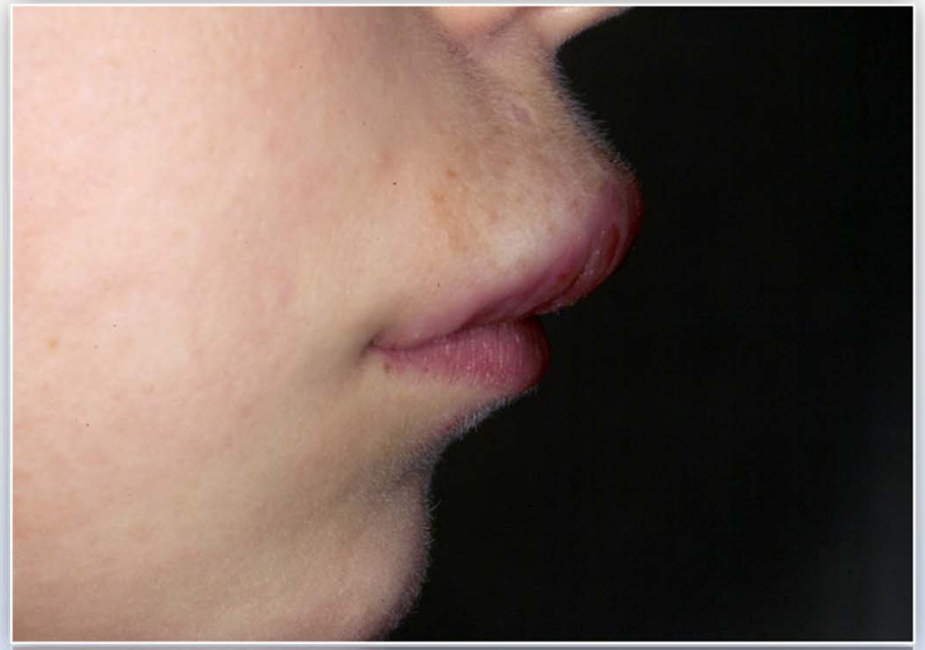

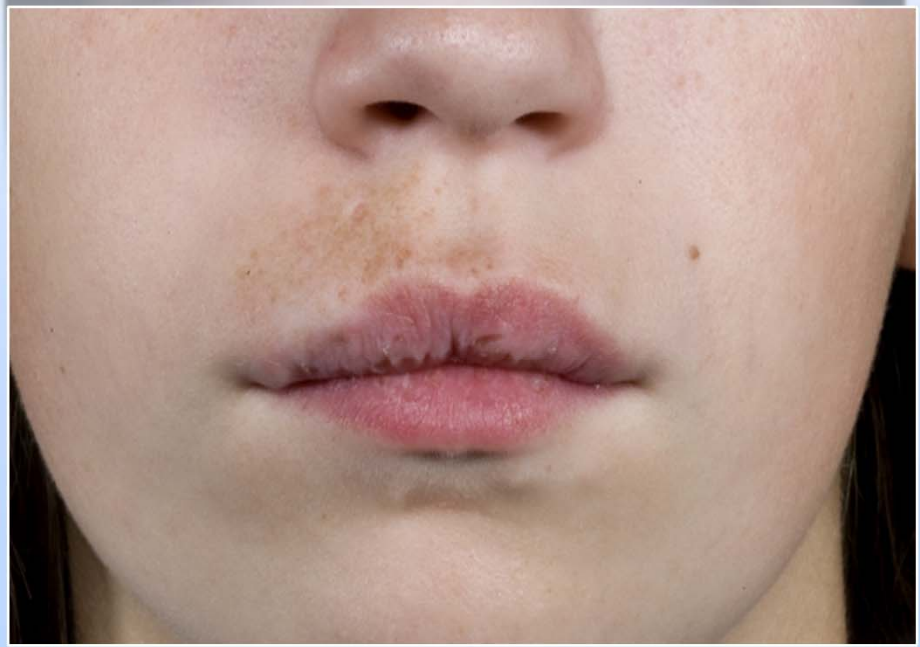

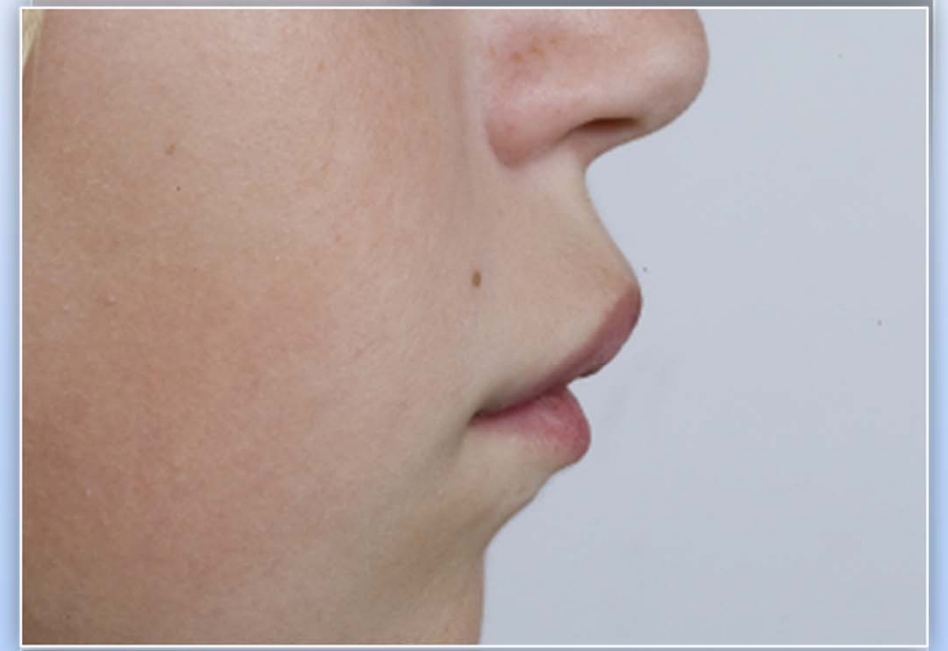

- Subtle aphthous ulceration and thickening of wall in recto-sigmoid junction

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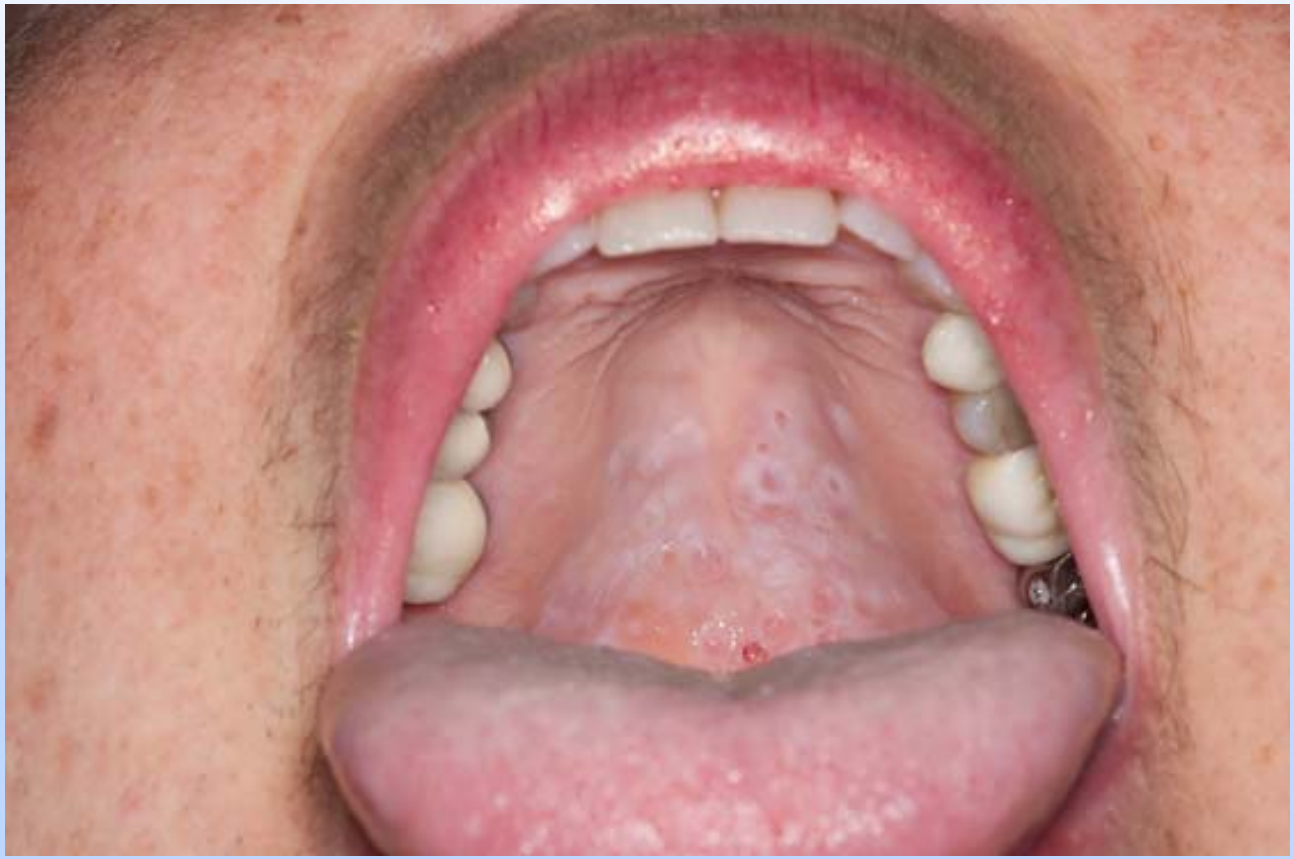
Case #2: 35 yo female S/P BMT for lymphoma

- Noticed these lesions, worse after eating



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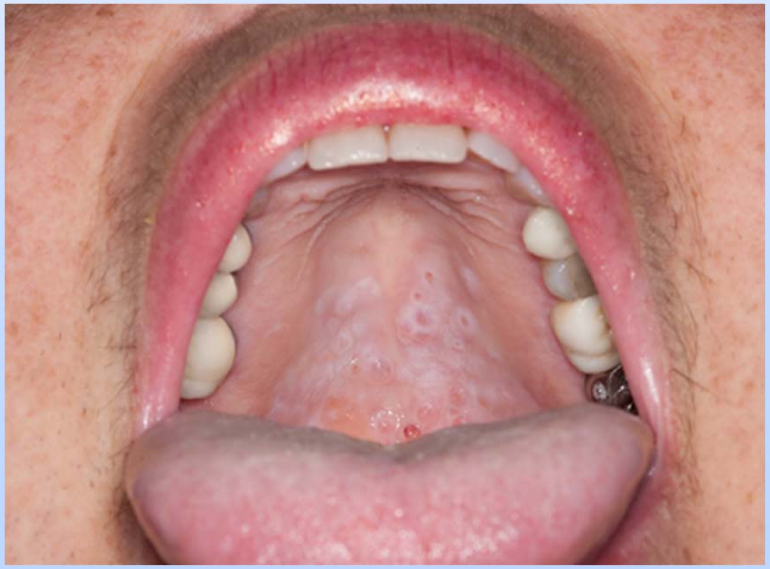
The most likely diagnosis is:

- Herpes stomatitis
- CMV infection
- Graft vs host disease
- Hand, foot and mouth disease
- Self induced vomiting



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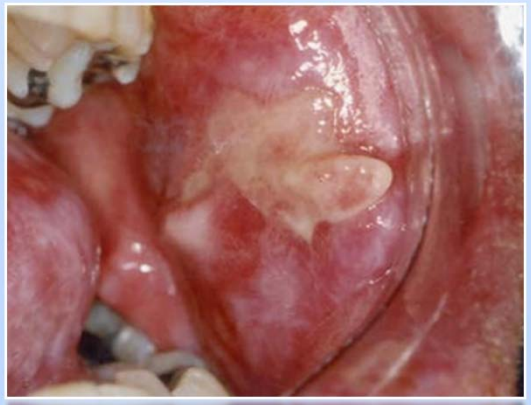
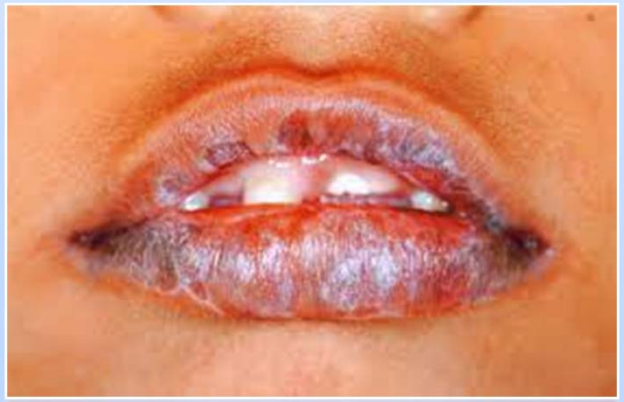
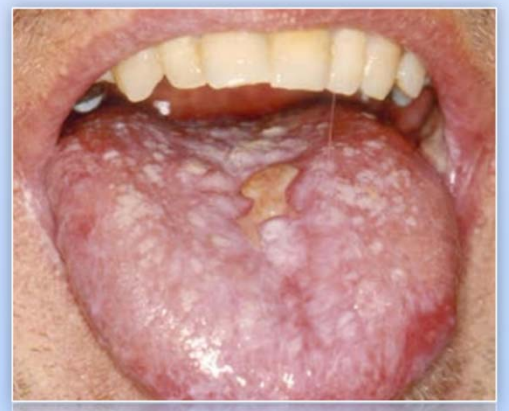
Oral Graft vs Host Disease

1. Mucosal Disease

- Lichenoid inflammation – tongue and buccal mucosa & lips frequent
- White hyperkeratosis reticulations/plaques
- Erythematous changes/atrophy
- Ulcerations (pseudomembrane)
- Risk of SCC







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Management – General

- Multisystem disease
  - Systemic therapy

- Duration of systemic therapy for cGVHD 2-3 yr; oral cGVHD require treatment long after systemic therapy

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Mucosal cGVHD:

Topical corticosteroids

- First-line therapy (based on expert opinion/descriptive studies)
- Solutions and gels best – hydrophilic & easily applied
- Most treatments off label/not FDA approved
- Dry mucosa with gauze
- Generalized/posterior disease - solutions
  - Dexamethasone solution 0.5 mg/5 mL – 5 mL, 5 min swish, gargle and spit; 4x/day for 2-4 wk
  - Clobetasol 0.05% solution (0.1 mg/mL)
- Budesonide solution(3mg/10mL)
  - Low bioavailability when absorbed through oral mucosa; limited systemic s/e*

*Gorouhi et al: Biol Blood Marrow Transplant, 1995

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Calcineurin Inhibitors

- Second-line therapy
- Tacrolimus ointment applied to dry surfaces
- Can be compounded as 0.1 mg/mL solution
- 2 - 4x day
- CNI may have  risk for epidermal malignancies; carcinogenic potential has to be considered
- Consider monitoring tacrolimus levels – esp. if concurrent Prograf

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Treatment

- "Ceiling" therapy
- Combine tacrolimus solution with clobetasol solution (1:1 mix) and apply up to 6x daily
- Dexamethasone rinse (0.5 mg/5 mL) + FK506 (0.5 mg/5 mL) also reported*
- Refractory cases – add or increase systemic immunosuppression
- Topical AZA – insufficient data
- ECPP may have good efficacy

*Mawardi et al: Bone Marrow Transplant, 2010

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2. Salivary Gland Disease

Xerostomia

Subtle and under recognized

- Salivary hypofunction
  - Significant with HCT conditioning, radiation
  - Salivary glands less affected by modern conditioning (non-myeloablative and non-radiation)*

*Treister et al: Biol Blood Marrow Transplant, 2005

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2. Salivary Gland Disease

- cGVHD - quantitative and qualitative changes production, composition and output
  - ↓ IgA and phosphate
  - ↑ Na, alb and IgG
  - ↓ serum and salivary IgA associated with oGVHD
- Saliva essential mastication, swallowing, taste, speech, tooth remineralization, maintaining pH
- ↑ Risk for candidiasis (esp. with topical steroid therapy); and tooth decay

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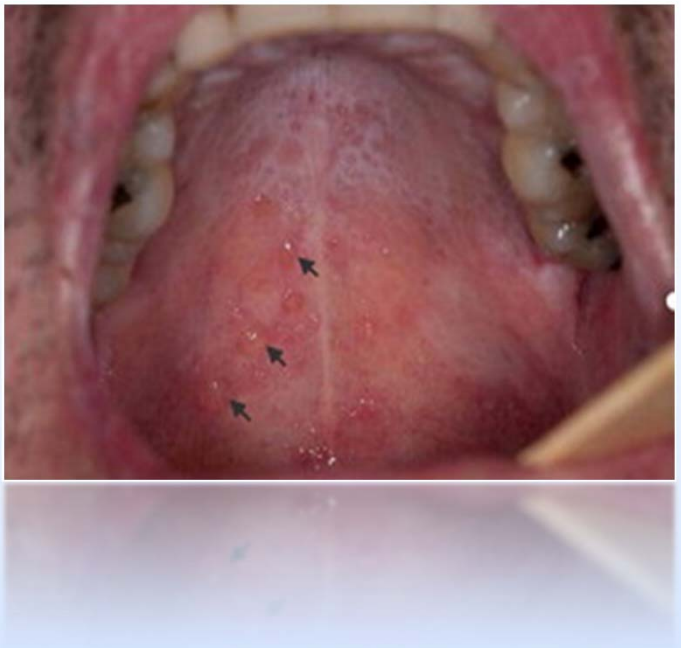
Mucoceles



- Inflammation and “leakiness” of minor salivary glands - ↓ amount and viscosity of saliva - blocks excretory ducts
- Recurrent superficial mucoceles – duct blocked forcing saliva into tissues
- Painless mucous-filled blisters

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Salivary Gland cGVHD

- Mucoceles
  - Usually asymptomatic; no intervention
  - Topical steroids may ↓ # & frequency
  - Surgery
- Xerostomia primary symptom – burning and sensitivity
  - Needs aggressive management
- Systemic immunosuppression not helpful for salivary cGVHD

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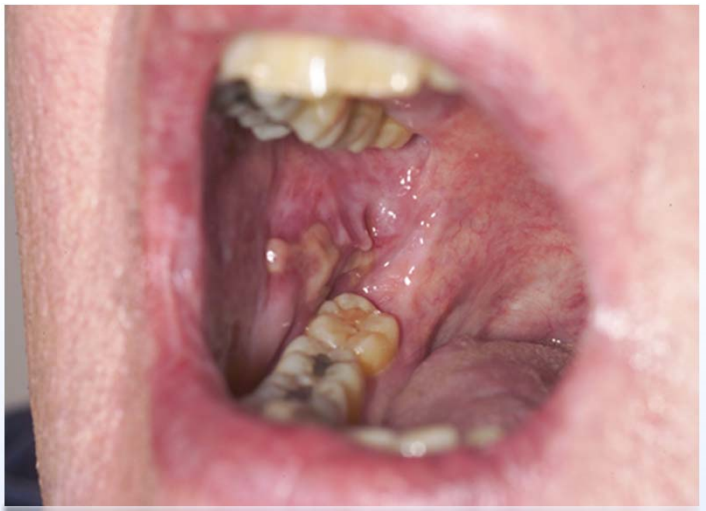
3. Sclerotic Disease



- Limited mouth opening, pain, ulceration
  ➡ impaired hygiene
  - Perioral sclerosis - extension of generalized sclerotic changes
  - Primary mucosal sclerosis d/t severe mucosal cGVHD ➡ band-like fibrosis in posterior buccal

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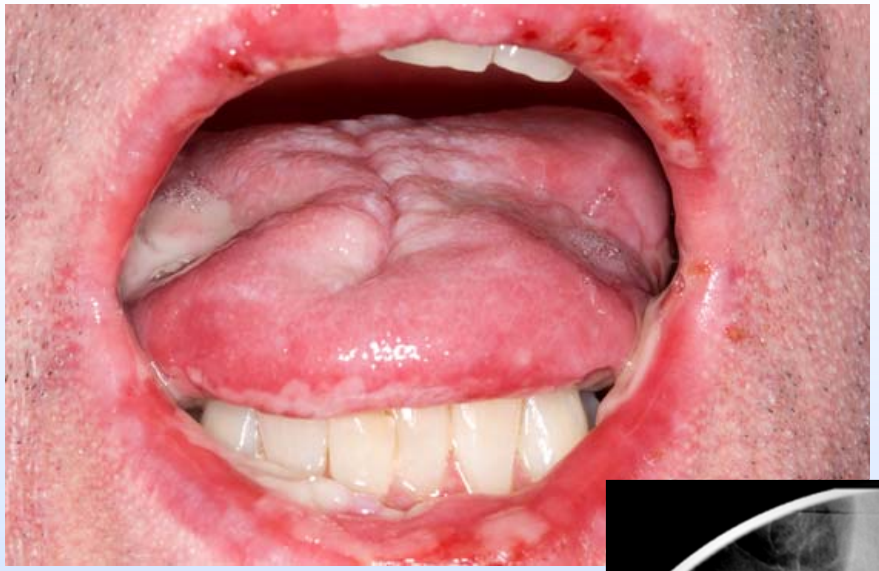
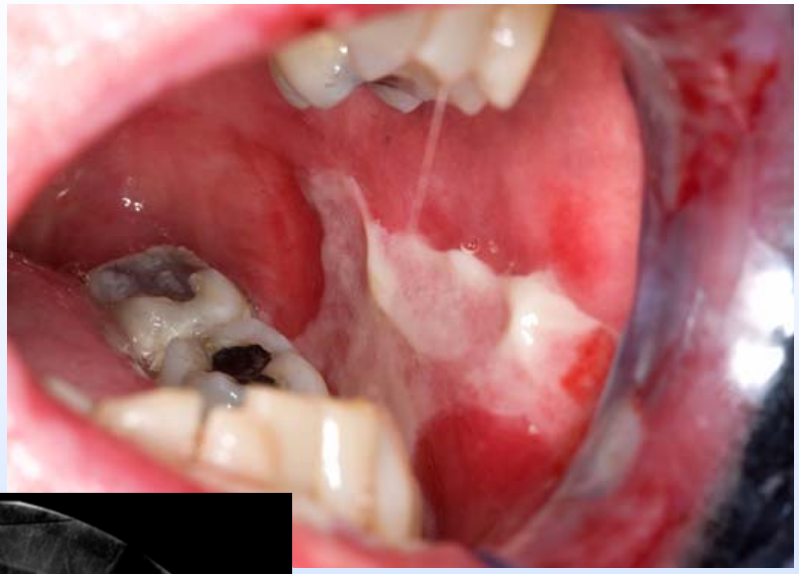
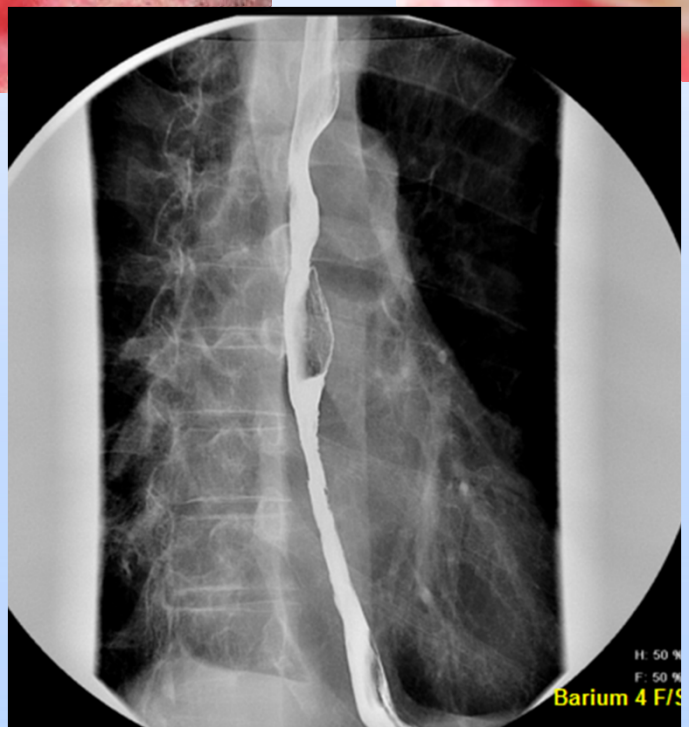
Case #3: 52 yo male dysphagia x yrs.
Oral lesions - lichenoid infiltrate on H&E and DIF







2009

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The best treatment is:

- Topical Protopic
- PO prednisone
- Methotrexate
- Hydroxychloroquine
- Systemic FK506 (tacrolimus)

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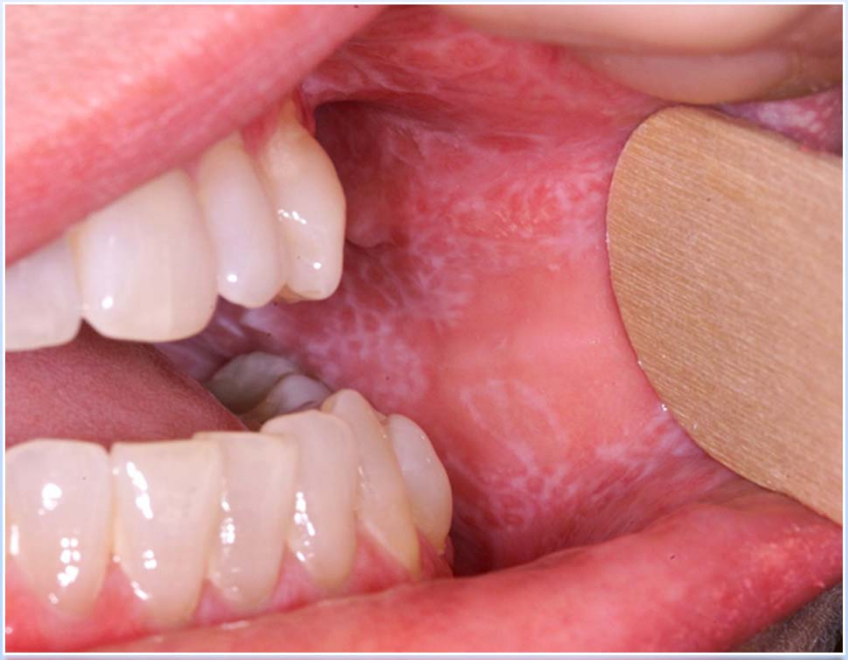
Lichen Planus

- ↑ Langerhans and dendritic cells → process and present foreign material to CD4+ lymphocytes → induce cytotoxic CD8+ lymphocytes → BMZ damage

- 3 types of lesions
  - Reticular
  - White (lace-like)
  - Asymptomatic



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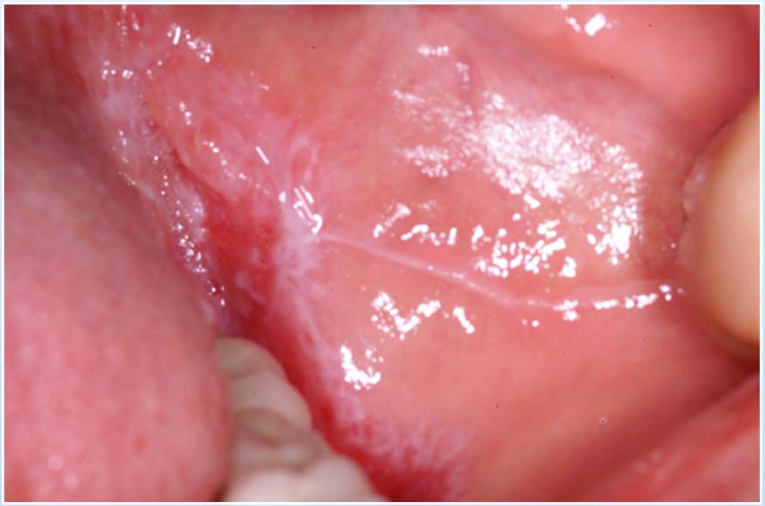
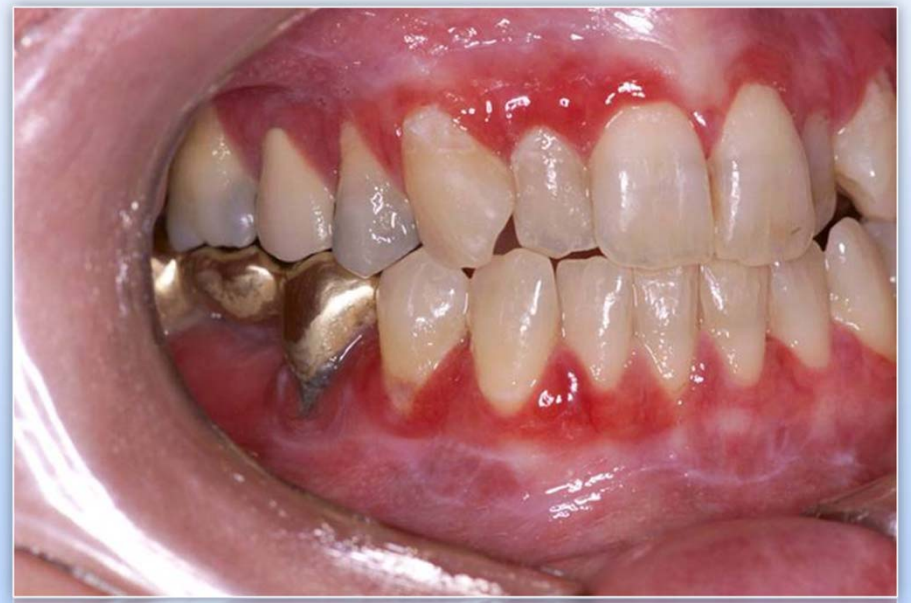
Clinical Appearance

Atrophic or erythematous

- Red, eroded plaques on mucosa





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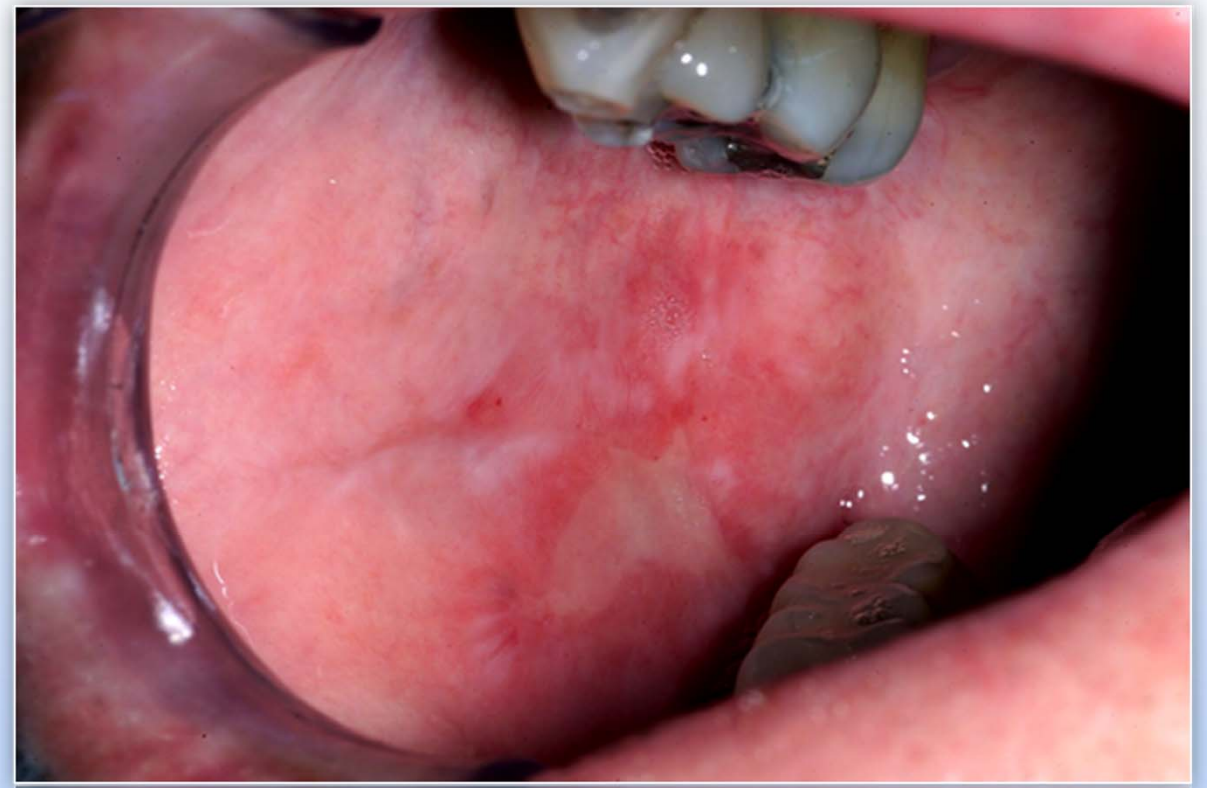
Clinical Appearance

Erosive

- Ulcerated, eroded areas
- Symptomatic
- SCARRING



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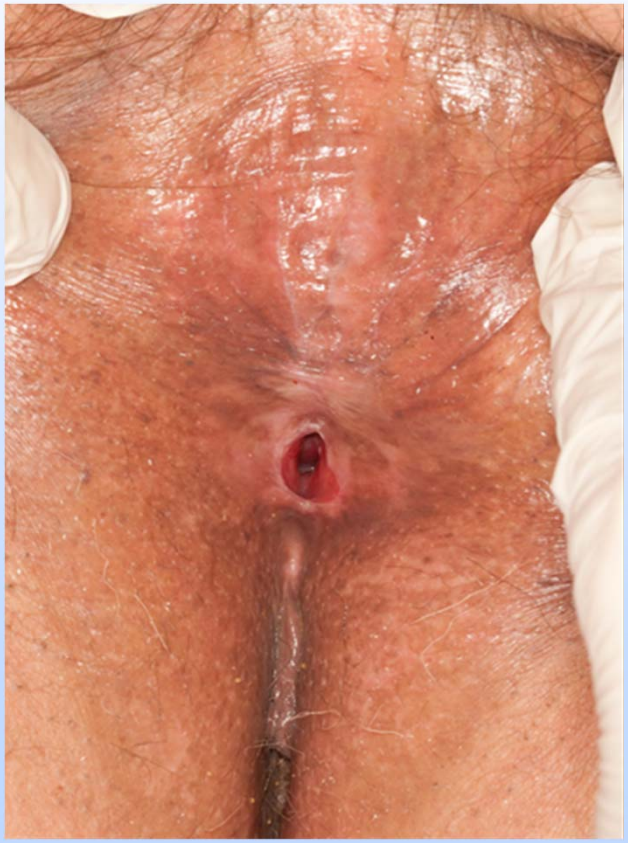
Genital Involvement

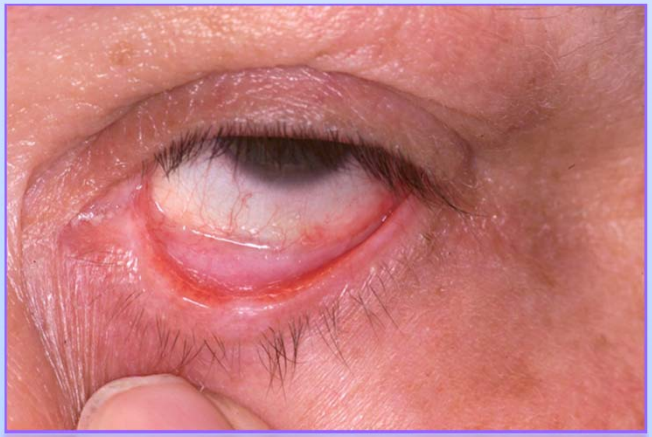
- Vulvovaginal-gingival syndrome
- Peno-gingival syndrome



MAYO CLINIC

Ocular Involvement

- Lichen planus and cicatricial conjunctivitis
  - Disease course and response to therapy of 11 pt*
- Cicatrizing conjunctivitis similar to that seen in MMP
- 8 pt had involvement of other mucosal sites



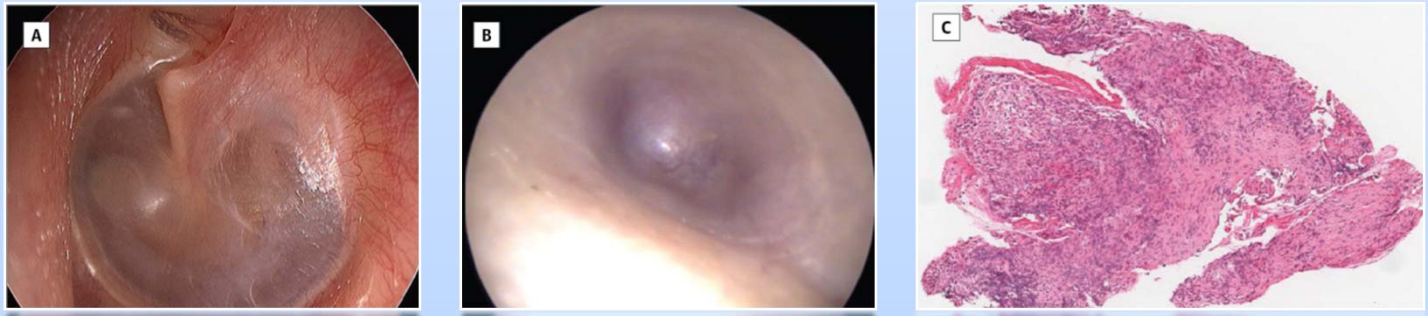
*Brewer et al: J Eur Acad Dermatol Venereol

MAYO CLINIC

Otic Involvement

10-yr review of otic lichen planus: The Mayo Clinic experience*

- 19 pt with otic LP; otorrhoea and hearing loss
- 5 had isolated otic disease
- Others multiple mucous membranes involved (mean 2.7 sites); most developed otic disease after LP diagnosed other sites; 1 pt otic involvement occurred first



*Sartori-Valinotti, Bruce, Krotova, Beatty

MAYO CLINIC

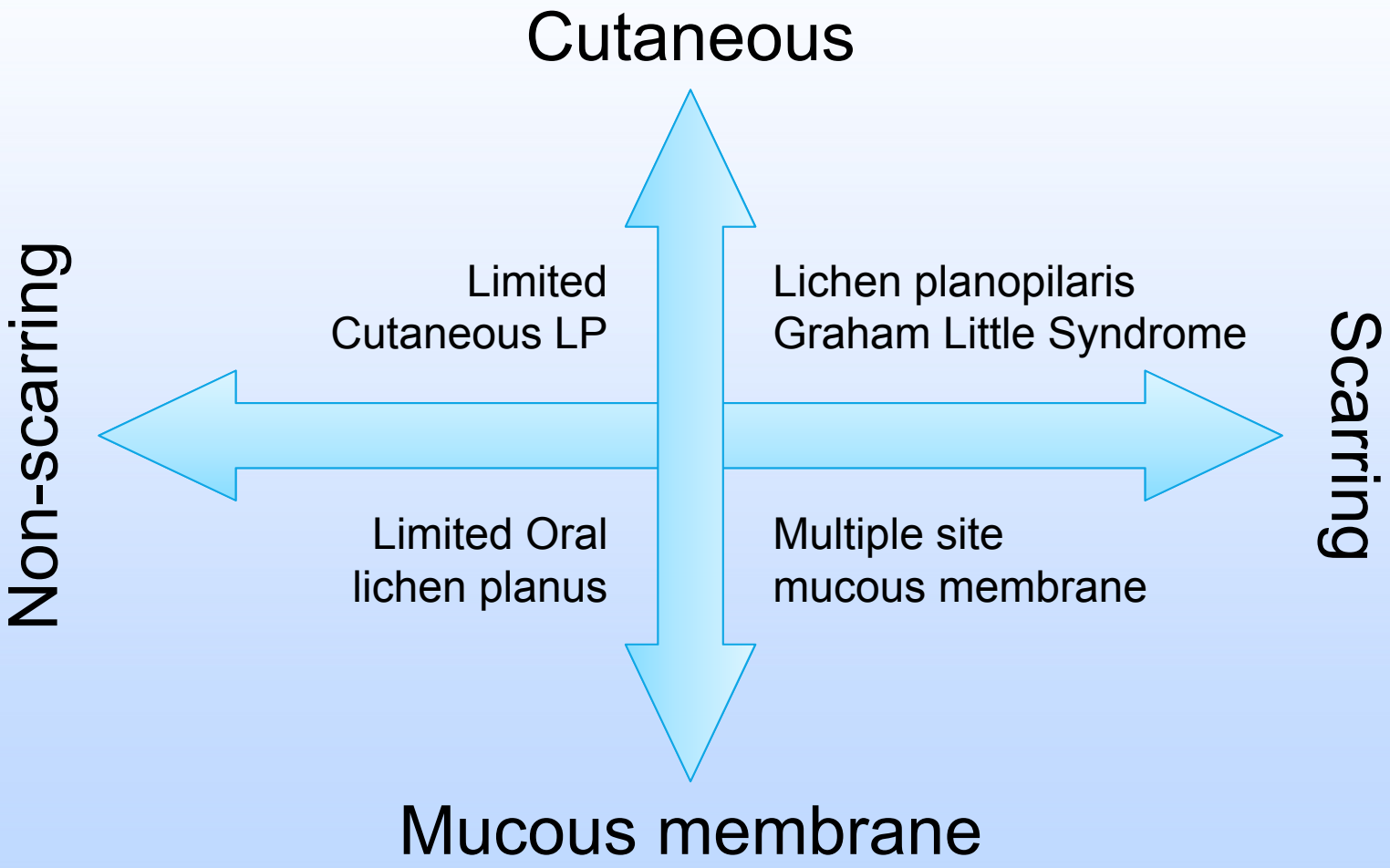
Esophageal Involvement

- 27 pt (25 female) *
- All presented with dysphagia, most had had multiple dilations
  - Half had esophageal LP as initial site; half had preexisting LP at other sites
  - 1 case esophageal LP developed 20 yr after initial dx
  - Oral (19); genital (13); skin (3)
- Challenging to treat

*Katzka et al: Clin Gastroenterol Hepatol, 2010

MAYO CLINIC

Mucocutaneous Lichen Planus



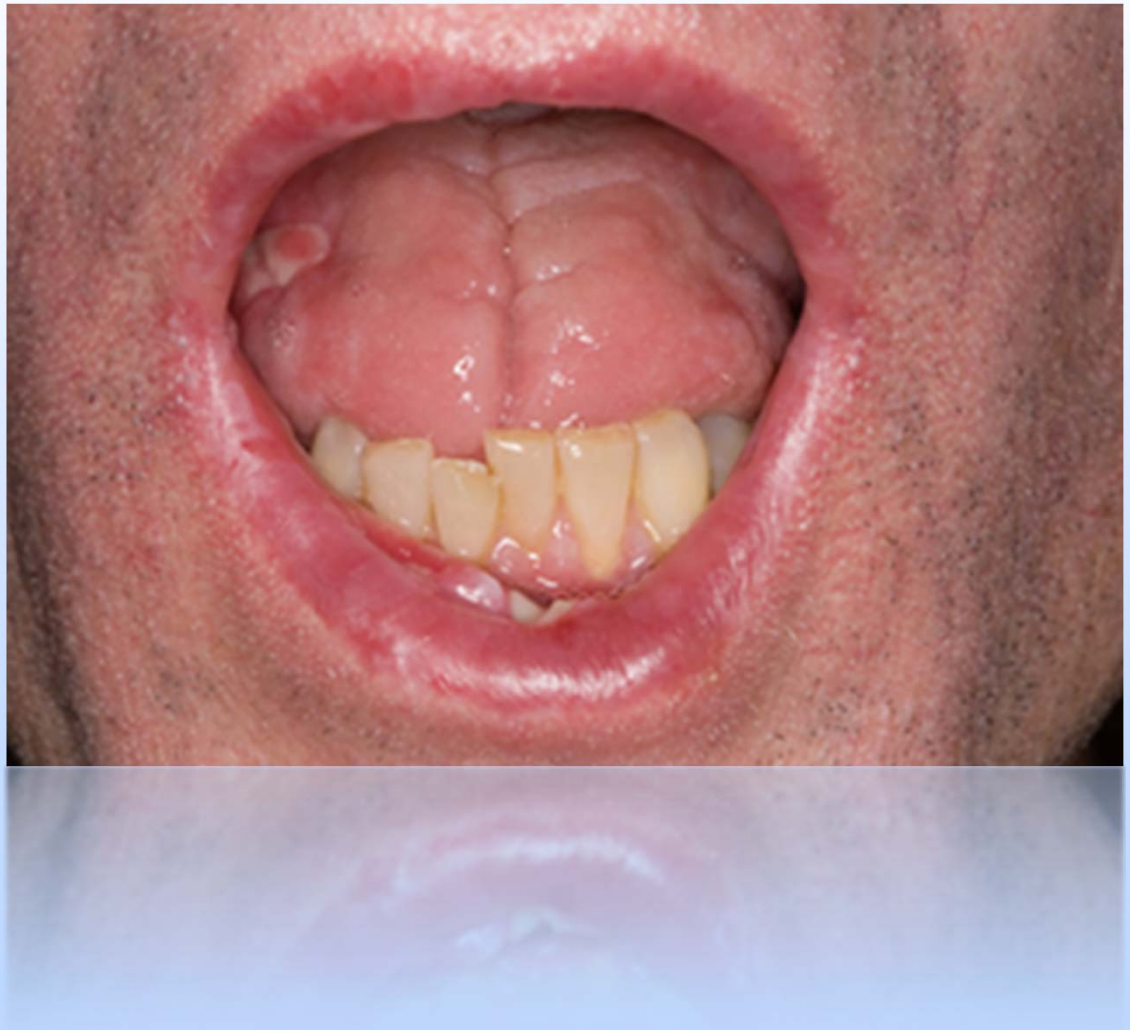
MAYO CLINIC

Treatment algorithm

- Topical therapy for mild to moderate disease
  - Corticosteroids
  - Calcineurin inhibitors (tacrolimus)
- Systemic therapy
  - Poorly responsive
  - Highly symptomatic
  - Organ at risk
- Options?
  - Methotrexate
  - Cellcept
  - Tacrolimus

MAYO CLINIC

2011 on MTX



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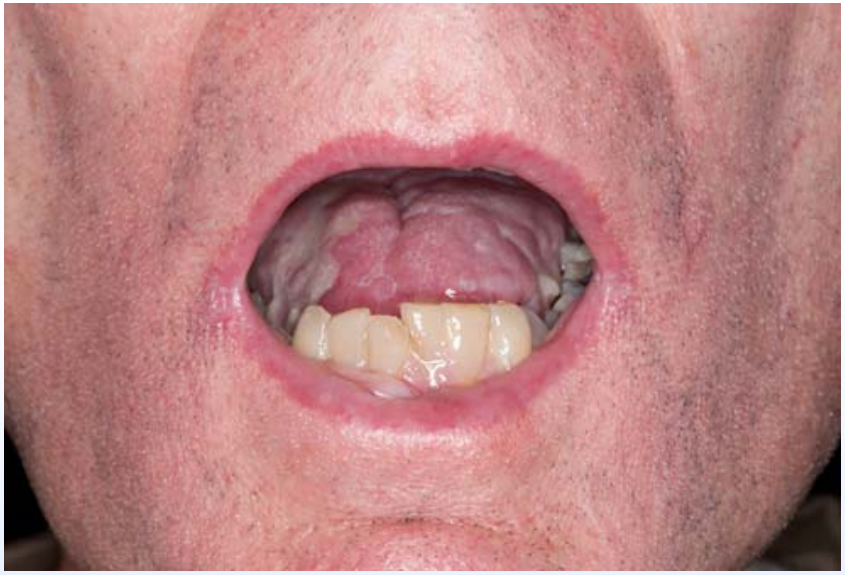
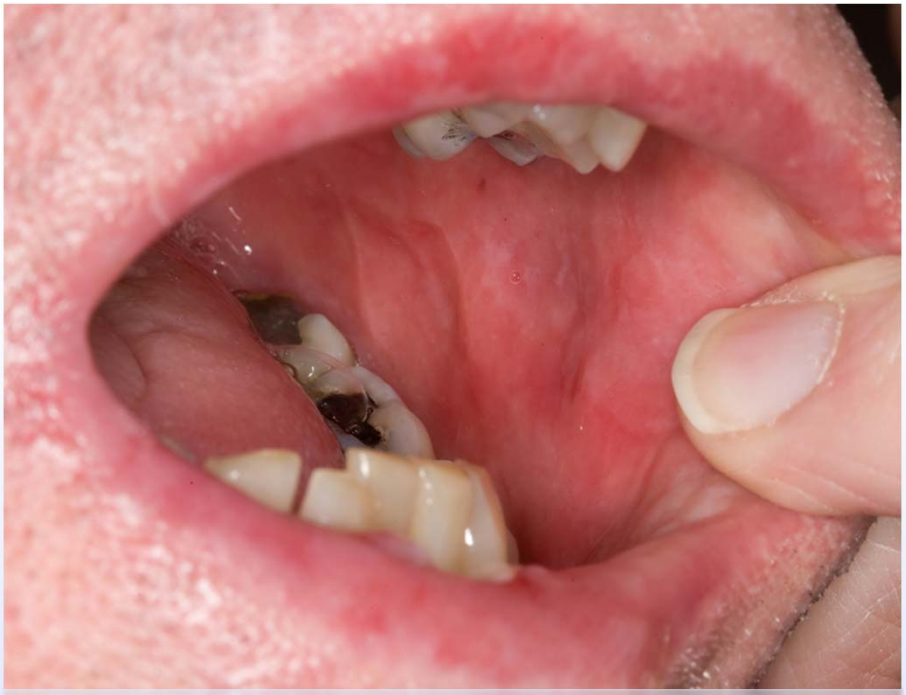
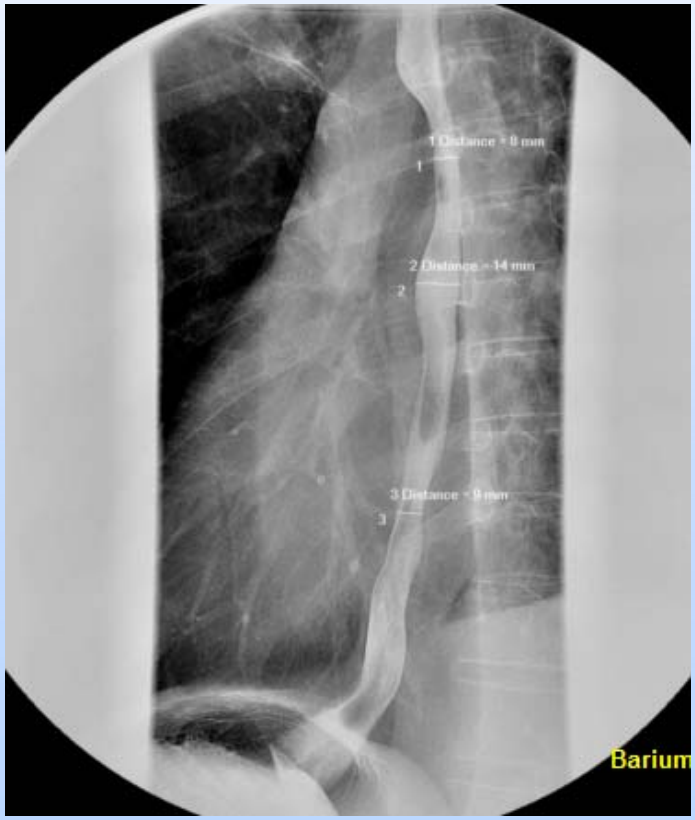


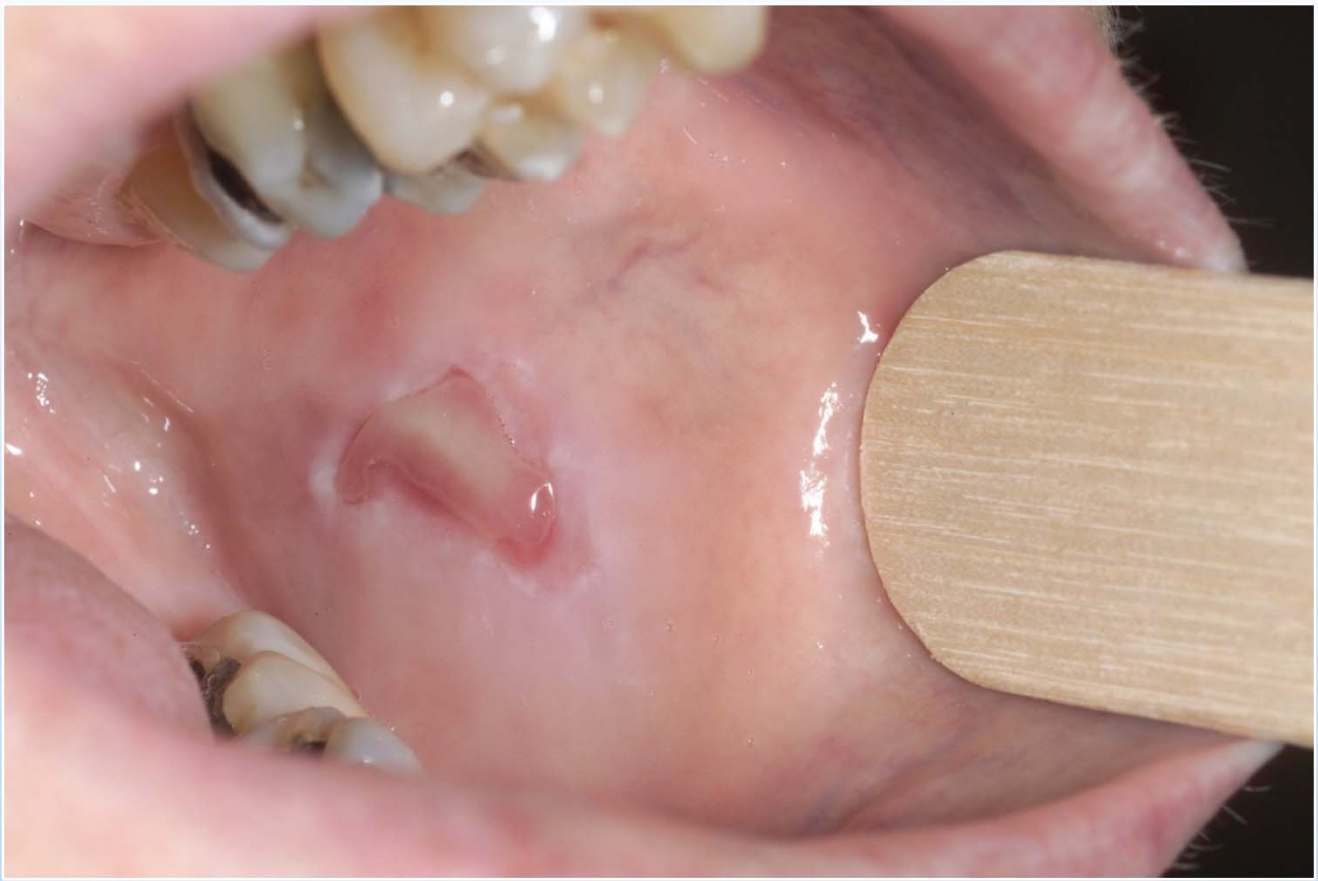




2014 on Tacrolimus

MAYO CLINIC

Case #4: This 56 yo female with stable LE on MTX, referred for 3 week hx of this ulcer:



MAYO CLINIC

The next best step is:

- Stop the MTX - drug induced ulcer
- She has a flare of LE - more aggressive systemic therapy
- Start PO prednisone
- Biopsy - oral cancer
- Refer her to a dentist

MAYO CLINIC

Oral Manifestations of Lupus Erythematosus

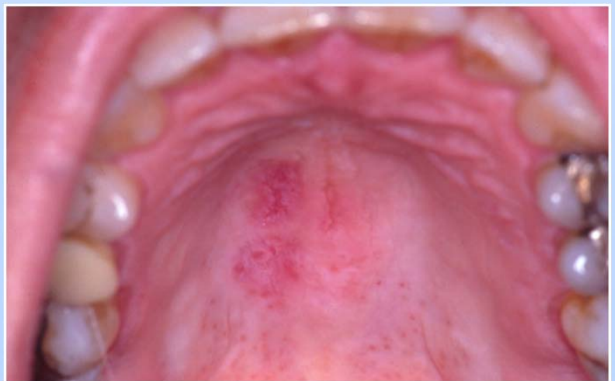
- Oral ulcers 1 of 4 derm ACR criteria
- Prevalence of oral lesions low ⟶ >50%
- ? More common in systemic (45%) vs cutaneous (20%) LE
- May be more prevalent in CLE*
- Certain alleles of STAT4 correlate with ↓ oral ulcers**

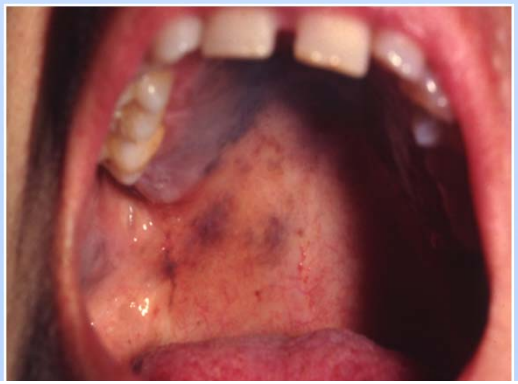
*Lourenco et al: J Cutan Path, 2007; **Taylor et al: PLoS Genet, 2008

MAYO CLINIC

Mucosal LE

- Oral lesions coexist / precede systemic & cutaneous LE
- Do not correlate with type of skin involvement or disease activity*
- More common in females
- Classic lesion
  - central erythema, white rim, keratotic striae at periphery with telangiectasia (<50%)

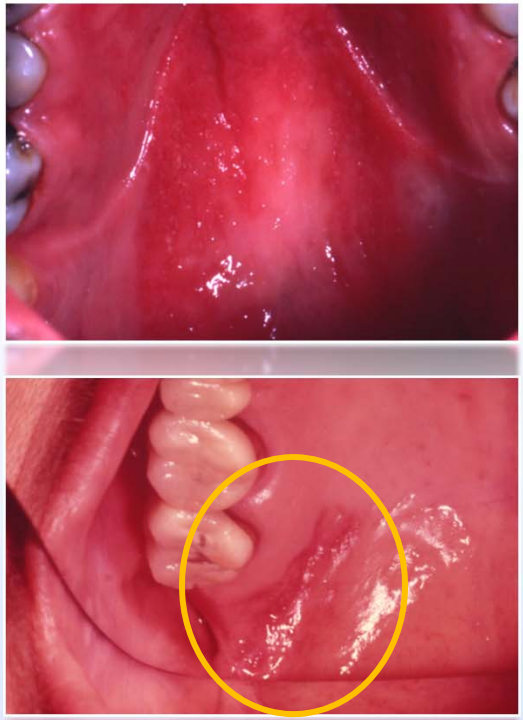




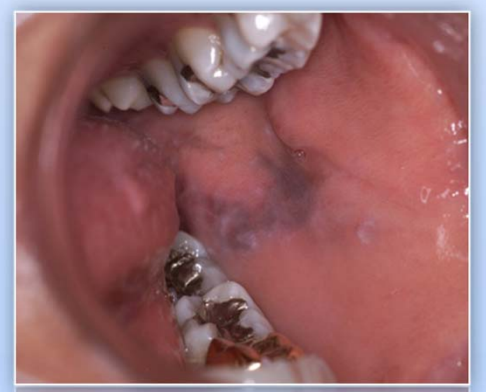
* Nico, Eur J Dermatol, 2008

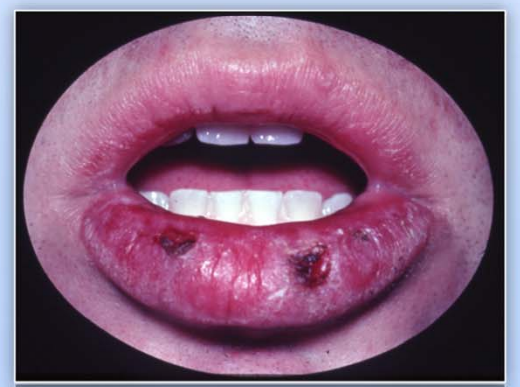
MAYO CLINIC

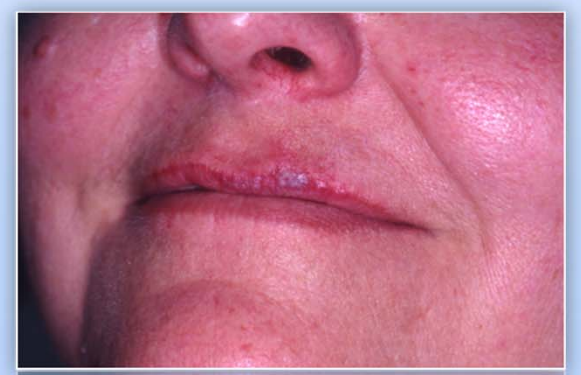
- Multiple & varied lesions
  - Erythematous lesions
  - Ulcers (painless)
  - LP-like, leukoplakia



- Sites: buccal > palate > vermilion(lower lip)

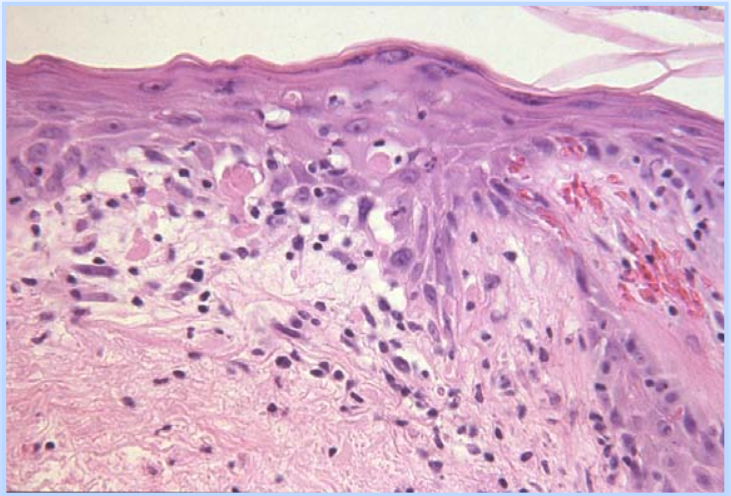




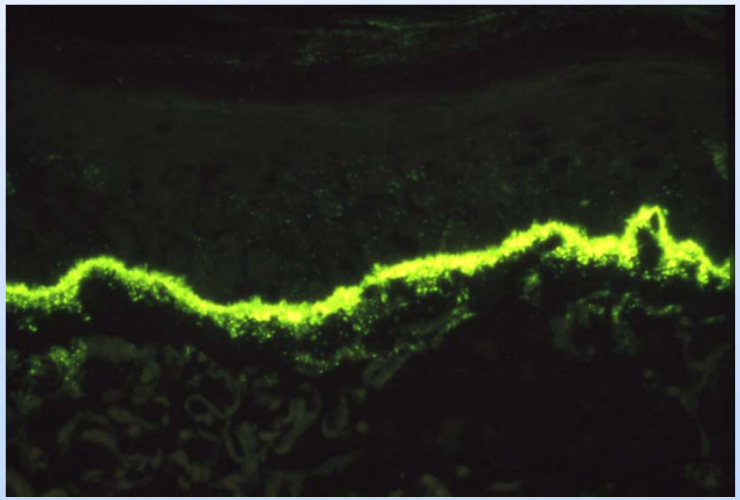


MAYO CLINIC

- Nasal ulcers - lower septum, bilateral, perforation rare
- Upper airway mucosa – hoarseness; conjunctiva and anogenital



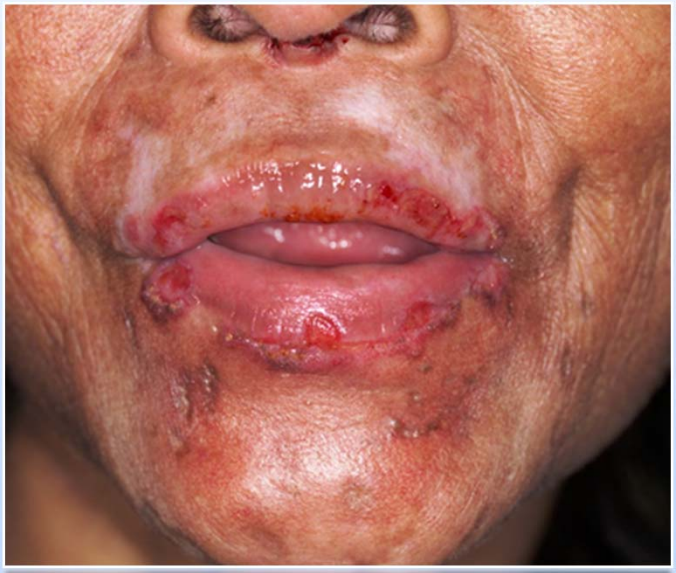
Lichenoid mucositis deep & perivascular infiltrate



DIF: Almost always + Linear IgG / C3

MAYO CLINIC

- May be premalignant – ulcerative / asymmetric lesions suspicious



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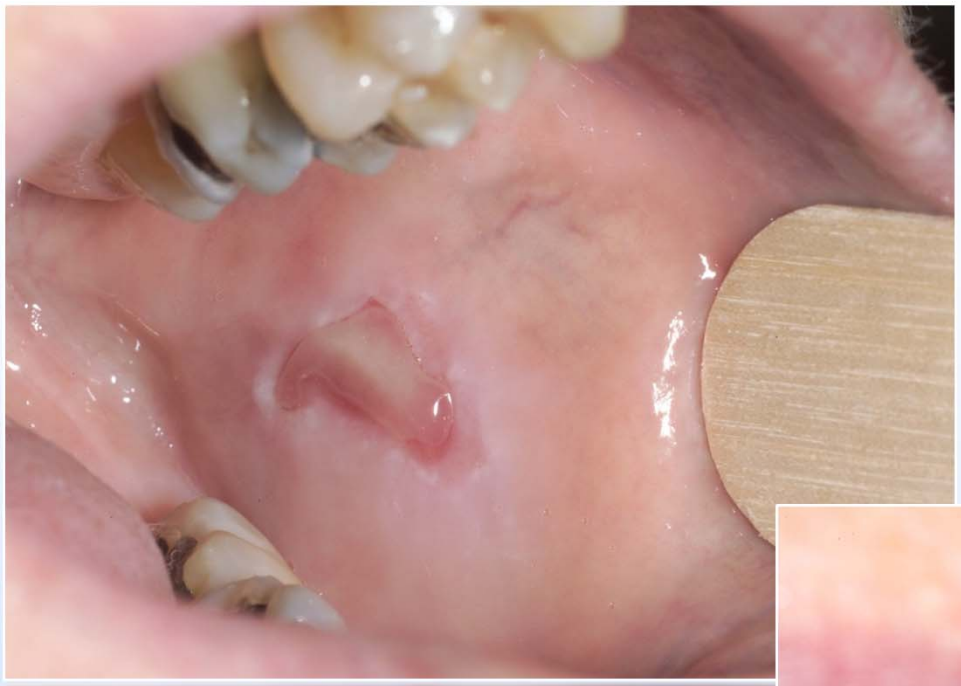
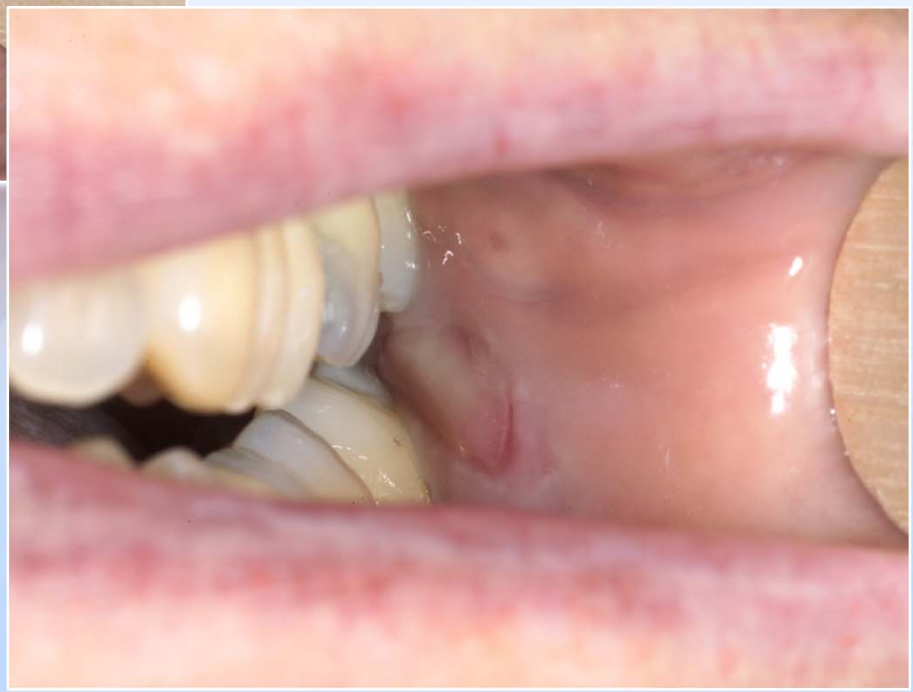




MAYO CLINIC

The next best step is:

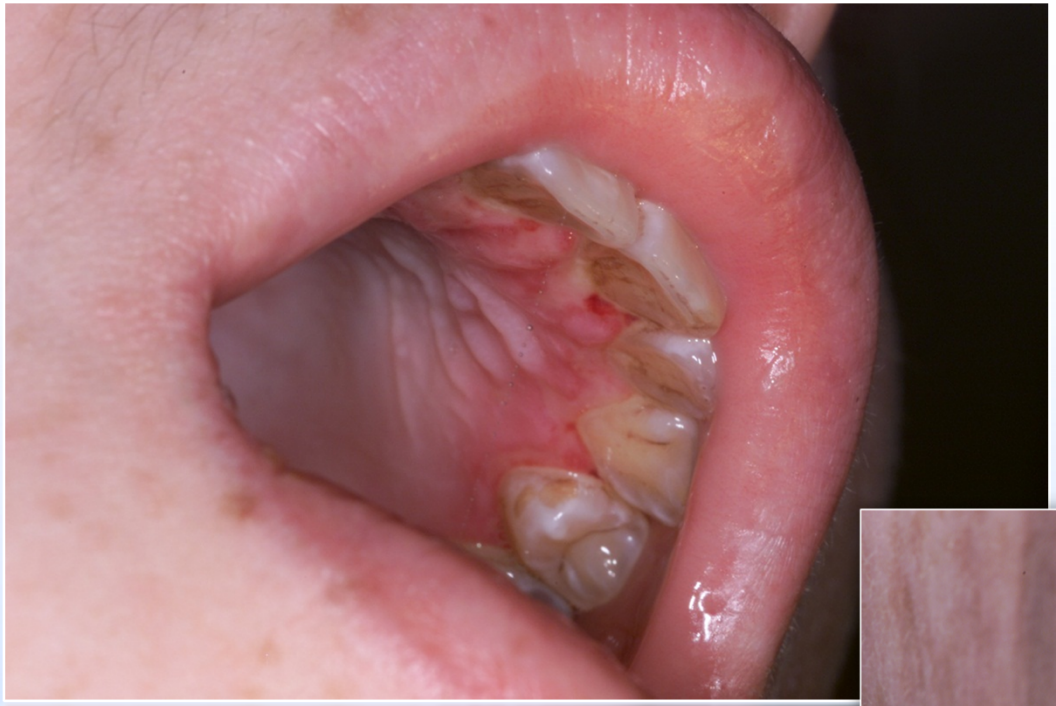
- Stop the MTX as this is a drug induced ulcer
- She likely has a flare of her LE and needs more aggressive systemic therapy
- Start PO prednisone
- Biopsy the lesion as this may represent oral cancer
- Refer her to a dentist

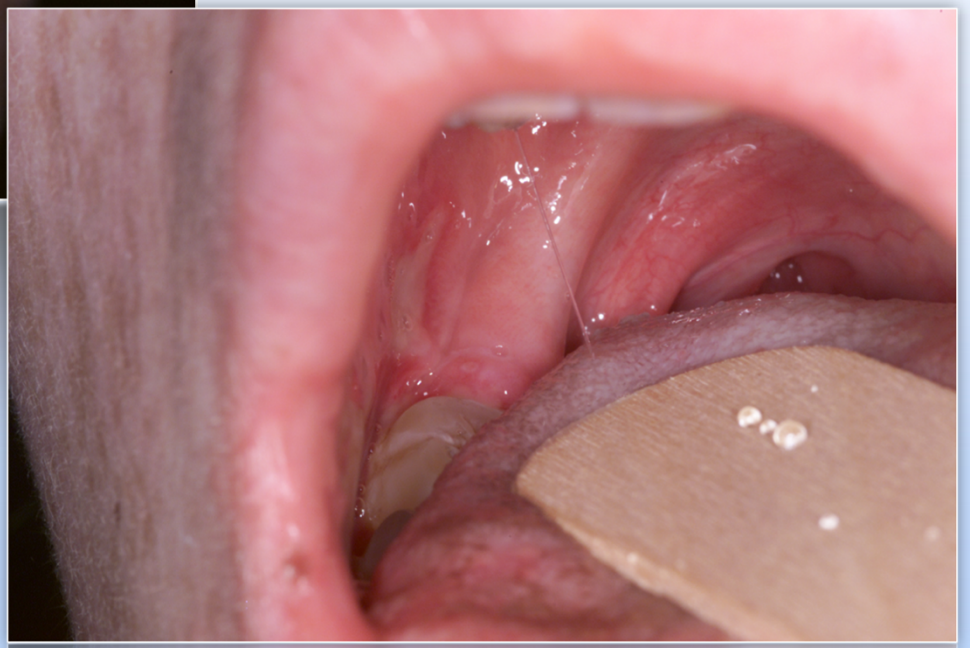
MAYO CLINIC

Ulcers in SLE

Examine the mouth carefully and look at morphology and function before making assumptions

MAYO CLINIC





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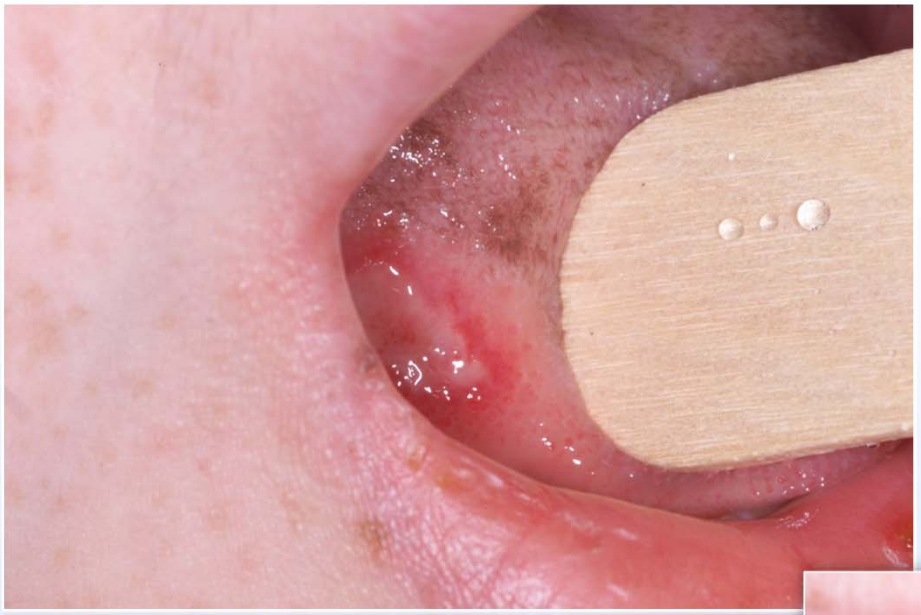
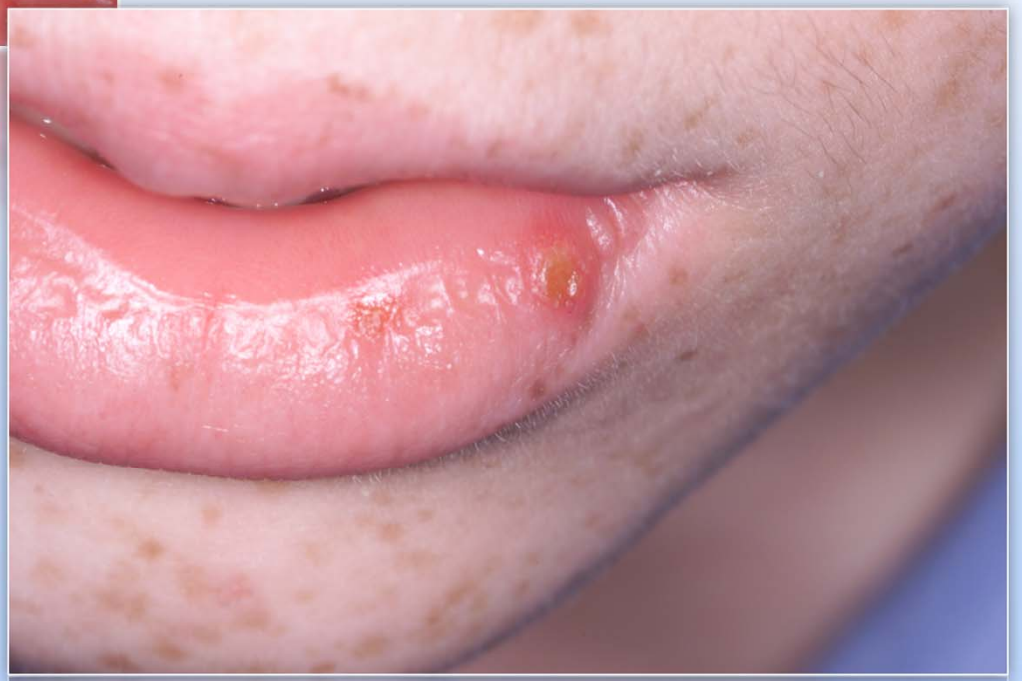
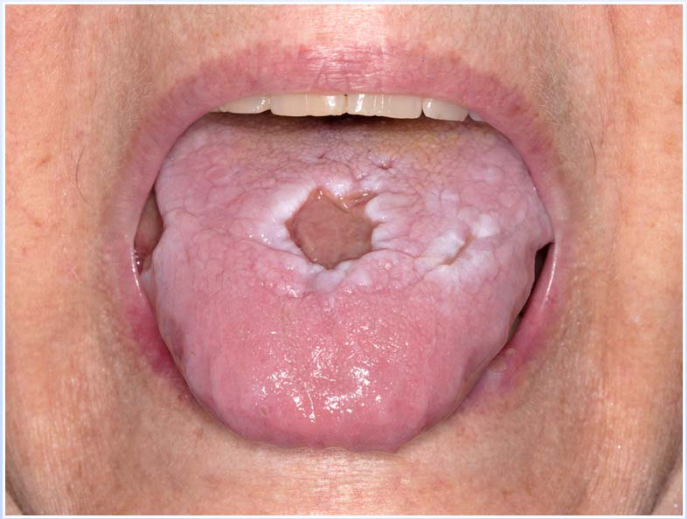
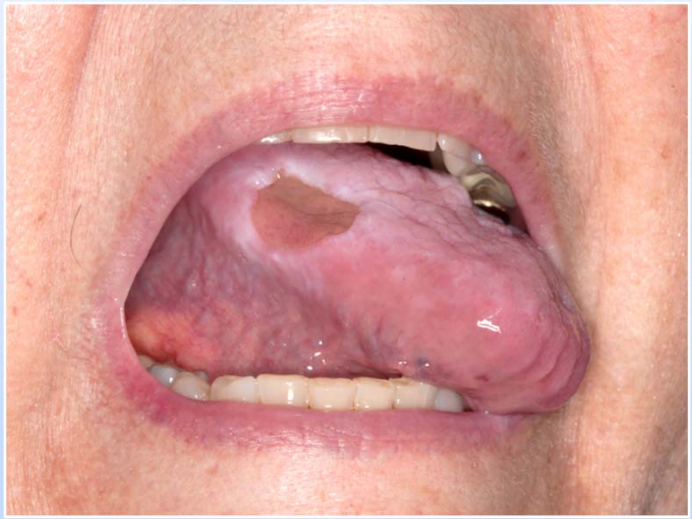




MAYO CLINIC

Case #5: 62 yo female with RSD, on long-term opiate meds, oral ulcers x 1 yr not responding to topical steroids





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The most likely diagnosis is:

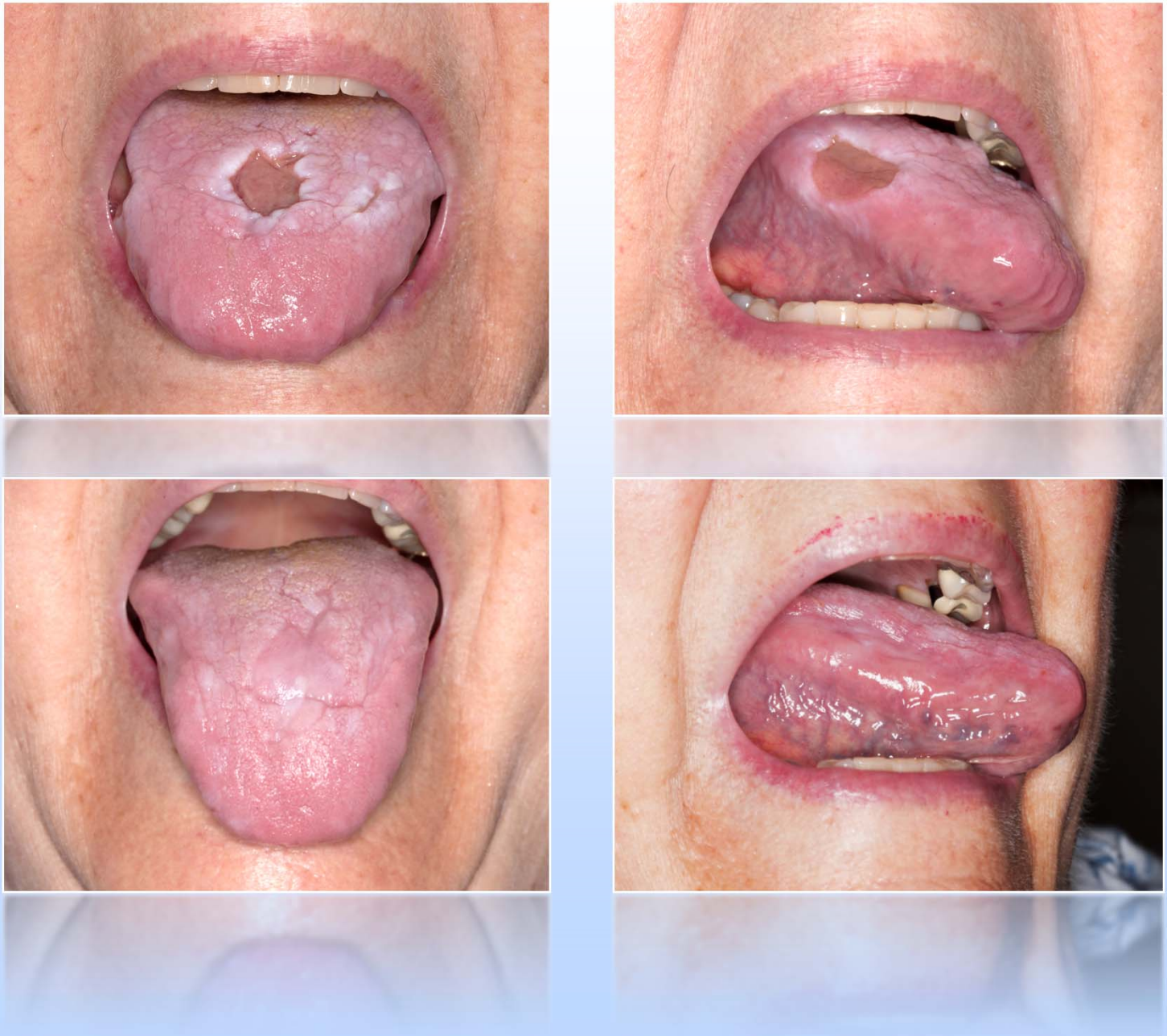
- Lichen planus
- SCC
- Pemphigus
- Cicatricial pemphigoid
- None of the above

MAYO CLINIC

Additional work-up

- Am cortisol: 1.5 (7 – 25)
  - Dexamethasone 0.67mcg/dL (<0.1)
- A1C: 6.9
- ↓ vitamin B6
- Candida +
- HSV 1 +
- Biopsy
  - ulcer with mixed stromal inflammation
  - DIF -
- Profound salivary hypofunction

MAYO CLINIC



MAYO CLINIC

Sjögren's Syndrome

- 0.5-5 % of population
- Females >>males (9:1)*
- Chronic lymphocytic infiltration of exocrine glands (salivary and lacrimal)
- Can occur alone (Primary SS)
- Association with CTD (Secondary SS) – RA commonest; SLE

*Mavragani: Autoimmun Rev, 2010

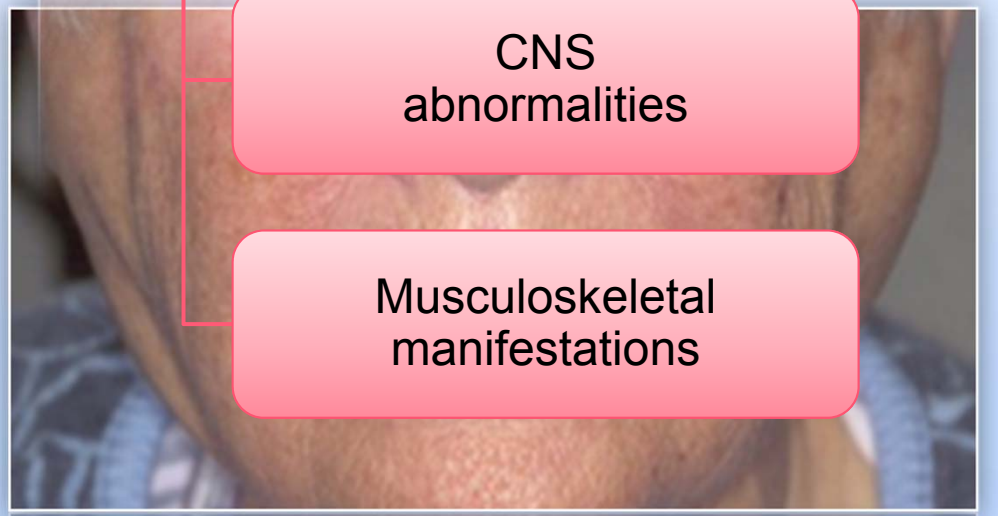
MAYO CLINIC

Exocrine gland
Sicca complex

- Xerostomia (oral dryness, decrease taste, change in oral flora)
- Keratoconjunctivitis sicca (gritty, sandy eyes)
- Parotid and other salivary gland enlargement
- Non specific cough
  Vaginal dryness

Extraglandular

- Skin: Xerosis, Vasculitis Raynaud's, Annular erythema
- Interstitial lung disease
- CNS abnormalities
- Musculoskeletal manifestations



Associated with ANA, SSA, SSB, RhF, cryoglobulins

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Sjogrens Syndrome
Spectrum of Disease Manifestation

Mild sicca symptoms;
low titer ANA;
vague fatigue and myalgias

Salivary gland enlargement;
LN; SSA, SSB Ab;
cryo; extraglandular involvement and propensity for NHL

MAYO CLINIC

Sicca symptoms

- = dry eyes + dry mouth
- Sicca symptoms >SS (35% older adults c/o dryness – age-related atrophy & drugs)
- Only 10% have objective evidence of reduced tear/saliva production

MAYO CLINIC

Tests to Quantify Xerostomia

- 4 tests (research)
  1. Sialography (duct cannulation with contrast)
  2. Scintography (technetium uptake)
  3. Salivary flow rates (whole sialometry)
     - Pt expectorates
     - Volume measured - 15 min (<1.5 mL positive)
  4. Saxon test (chews gauze sponge for 2 min; change in weight)

Difficulty swallowing dry food ("cracker test")

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Diagnosis
Criteria

American-European Consensus Group (AECG) (not routine clinical practice)

- Subjective
  - Ocular symptoms
  - Oral symptoms
- Objective
  - Signs of corneal damage
  - + tests impaired salivary gland function
  - Salivary gland bx
  - + autoantibodies
- 4 of 6; with + histo or serology (hi sensitivity and specificity)
- 3 of 4 objective criteria (lower sensitivity)
- Secondary SS – CTD plus combination of above

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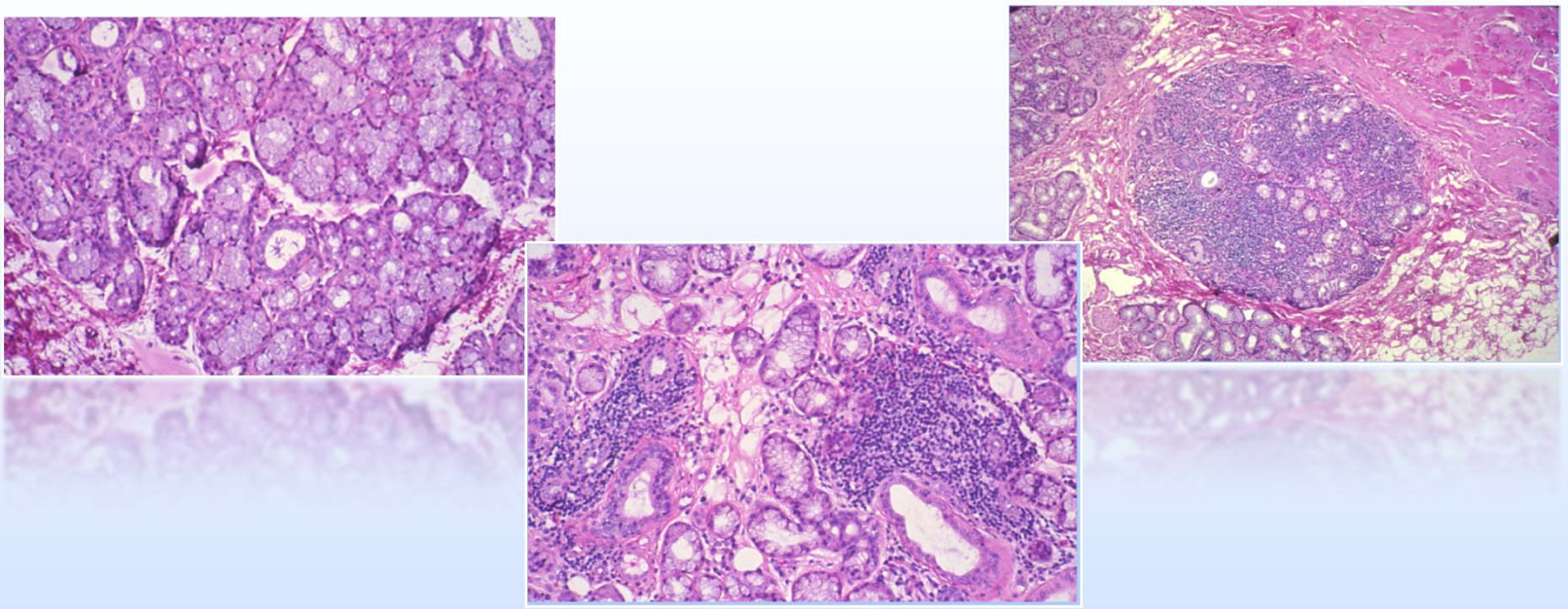
Labial salivary gland biopsy



- Bx - 4 lobules of salivary gland tissue
- Grade no. of foci (>50 lymphocytes / 4 mm^2) of lymphoid tissue
- More than 1 foci defined for SS

MAYO CLINIC

American College of Rheumatology 2012

- For clinical trials; no distinction between 1° or 2°
- 2 of 3 (objective)
  - SSS and/or SSB; or RHF and ANA >1:320
  - Ocular staining score >3
  - Bx: lymphocytic sialadenitis with >focus/4 mm
- Pt with ≥4 criteria from AECG probably have SS

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Dental Care

- Daily brushing, including
  - Avoid SLS & flavored toothpastes
  - Antibacterial mouthwash – avoid alcohol or phenol
    - Alcohol-free chlorhexidine gluconate oral rinse USP; 0.12% from GUM

MAYO CLINIC

SS Treatment
Managing dryness

- Regular sips of water (rinsed & expectorated)
- Excessive sipping can reduce mucous film
- Avoid low pH (acidic) drinks
  - Cola: pH 2.6
  - Coffee: pH 5.0
  - Herbal tea: pH 3.2
  - Black tea: pH 5.7-7.0
  - Tap water: pH 7.0 (flavored acidic)
  - Energy drinks: Usually acidic
- Maintaining stable pH avoids demineralization
- Taste disturbance: sodium bicarb solution

MAYO CLINIC

Sodium bicarbonate mouth rinse

- Half teaspoon bicarb in glass of water BID
- Helps control infection
- Analgesic (due to its buffer action)

MAYO CLINIC

Topical salivary stimulants

- Sugar-free gum/candy (not sugarless, this contains fructose - is cariogenic)
- Acid-free; not lemon, orange or citric flavoring
- Gum or candy with Xylitol (reduces cariogenicity of oral bacteria) or Recaldent
- Dried fruit slices (peaches)

MAYO CLINIC

Saliva substitutes

- Various components and viscosity → try several
- Carboxymethylcellulose, polyethylene glycol sorbitol and electrolyte
- Mix and match
  - Spray before speaking
  - Solution before eating to aid swallowing
  - Gel before bedtime (Xylimelts discs)

MAYO CLINIC

Sialagogue therapy

- 50% pt respond
- Response may take 8-12 wk; usually improvement within 1-2 wk
  - Pilocarpine (Salagen) 5 mg tid
  - Cimevuline (Evoxac) 30mg tid
- After 8 wk dose can be increased
- Contraindicated asthma d/t (or pulmonary GVHD) increased secretions
- Helpful for xeropthalmia

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Conclusion

- OFG – look for IBD in young pts
- Be familiar with oral GVHD
- Treat widespread mucosal LP aggressively
- Evaluate oral lesions in pts with LE carefully
- Recognize and treat xerostomia

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