Oral Manifestations of Auto-Inflammatory Disease

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DISCLOSURES

The content of this presentation does not relate to any product of a commercial interest; therefore, there are no relevant financial relationships to disclose.
Venus Williams has Sjogren's Syndrome: What is it?
CBC news
Case #1: 10 yo female

- 3 weeks hx of painless left sided facial swelling
- Negative ROS
- Normal labs (CBC, ESR, chem)
The best diagnostic test is:

- Fine needle aspirate of swelling
- MRI of face and parotid gland
- Colonoscopy
- Bone scan
- Panoramic dental X-ray
Treated with PO clindamycin
Developed C diff infection
Swelling persisted
- MR enterography normal
- Upper endoscopy and colonoscopy - GRANULOMAS

- Dx: Crohns disease
- Commenced treatment with Azathioprine
- Complete remission 1 yr later
The best diagnostic test is:

- Fine needle aspirate of swelling
- MRI of face and parotid gland
- Colonoscopy
- Bone scan
- Panoramic dental X-ray
Oral signs in Crohn's Disease

Specific
• Granulomas

Non-specific
• Aphthous ulcers
• Pyostomatitis vegetans
Oral Features

- Lips
  - Labial enlargement
Lips

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

• Midline fissuring (median cheilitis)

• Fissuring at angles of mouth (angular cheilitis)
Intraoral Mucosa

Mucosal swelling

• Rugae of intra-oral mucosa
Staghorn Sign
Intraoral Mucosa

Cobblestoning

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

Ulcers

• Most common – chronic, deep in buccal or labial vestibule with raised borders
Intraoral Mucosa

Mucosal Tags

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

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

• Fissuring
Tongue

- Swelling
Non-specific manifestations (reactive)

Major Aphthous Ulcers with Crohn's Disease
Pyostomatitis Vegetans

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

- Persistent swelling – characteristically lips
- Granulomas + lymphedema

Etiology
- Idiopathic
- Sarcoid
- Infection (mycobacterial)
- Allergy (dental mental/food)
- IBD
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
Clinical Markers

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

Orofacial

OFG

OFG + gut involvement

Oral Crohn’s + GI Crohn’s

Gut

Crohn’s
Case

13 yr girl with several year hx swollen upper lip
Treated with sclerotherapy for presumed lymphangioma
Granulomatous Cheilitis

- Biopsy – non caseating granuloma
- No associated disease identified
- Treated with doxycycline as anti-inflammatory
- 6 weekly IL corticosteroid over 6 mos
Outcome
Is orofacial granulomatosis in children a feature of Crohn's disease?

Khouri JM¹, Bohane TD, Day AS.

Abstract
We present six children presenting with orofacial granulomatosis at an early age (range 5-8 y) whose course points towards the development of Crohn's disease

CONCLUSION:
Orofacial granulomatosis in the paediatric population may be an initial manifestation of Crohn's disease and so careful surveillance is recommended.
• “Subtle changes including aphthous ulceration, and thickening of the bowel wall in the recto-sigmoidal region”

• GI did not feel conclusive evidence of Crohn's disease - close follow up
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
Case #2: 35 yo female S/P BMT for lymphoma

- Noticed these lesions, worse after eating
The most likely diagnosis is:

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

1. Mucosal Disease

- Lichenoid inflammation – tongue, buccal mucosa & lips
- White hyperkeratosis reticulations/plaques
- Erythematous changes/atrophy
- Ulcerations (pseudomembrane)
- **Risk of SCC**
Mucosal cGVHD:

Topical corticosteroids

- First-line therapy (expert opinion/descriptive studies)
- Solutions and gels best – hydrophilic & easily applied
- Most treatments off label/not FDA approved
- Dry 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 through oral mucosa; limited systemic s/e

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 be considered
- Consider monitoring tacrolimus levels – esp. if concurrent Prograf
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
2. Salivary gland disease

- Salivary gland involvement less obvious & under recognized
- Xerostomia significant - esp. HSCT conditioning total body, or H & N radiation
- Recent studies - salivary glands less affected by modern conditioning (non myelo-ablative, & non radiation)*

*Treister et al, Biol Blood Marrow Transplant, 2005
2. Salivary gland disease

- cGVHD produces quantitative and qualitative changes in production, composition
  - ↓ IgA and phosphate
  - ↑ Na, alb and IgG
  - depressed serum and salivary IgA positively associated with development of GVHD
• **Xerostomia**

• Common to encounter pts. with xerostomia - normal clinical findings – suggesting qualitative changes

• ↑ risk for candidiasis (esp. if ongoing topical steroid therapy), and tooth decay
Mucoceles

- Inflammation and “leakiness” of minor salivary glands - ↓ amount and viscosity of saliva - blocks excretory ducts
- Recurrent mucoceles – duct blocked forcing saliva into tissues
- Painless mucous-filled blisters
• **Mucoceles**
  
  • Present acutely when eating
  • Complete resolution shortly after - mainly nuisance
  • Must be differentiated from HSV
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
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
Case #3: 52 yo male dysphagia x yrs. Oral lesions - lichenoid infiltrate on H&E and DIF
The best treatment is:

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

Atrophic or erythematous

- Red, eroded plaques on mucosa
Clinical Appearance

Erosive

• Ulcerated, eroded areas
• Symptomatic
• SCARRING
Genital Involvement

- Vulvovaginal-gingival syndrome
- Peno-gingival syndrome
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
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

*Sartori-Valinotti, Bruce, Krotova, Beatty
Esophageal Involvement

• 27 pt (25 female) *

• All presented with dysphagia, most 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
Mucocutaneous Lichen Planus

Cutaneous

Non-scarring

Limited Cutaneous LP

Limited Oral lichen planus

Mucous membrane

Scarring

Lichen planopilaris Graham Little Syndrome

Multiple site mucous membrane
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
2011 on MTX
2014 - Tacrolimus
2015 - Soriatane
Mucocutaneous Lichen Planus With Esophageal Involvement
Successful Treatment With an Anti-CD20 Monoclonal Antibody

Laurent Parmentier, MD, PhD; Blaise-Alain Bron, MD; Christa Prins, MD; Jacky Samson, MD; Isabelle Masouyé, MD; Luca Borradori, MD
An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: A case series

Joan Paul, MD, MPH\textsuperscript{a} • ©, Clare E. Foss, MD\textsuperscript{b}, Stefanie A. Hirano, MD\textsuperscript{b}, Tina D. Cunningham, PhD\textsuperscript{c}, David M. Pariser, MD\textsuperscript{a, b}
Case #4: This 56 yo female with stable LE on MTX, referred for 3 week hx of this ulcer:
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
Oral Manifestations of Lupus Erythematosus

- Oral ulcers 1 of 4 derm ACR criteria
- Prevalence of oral lesions low $\rightarrow >50\%$
- ? More common in systemic (45%) vs cutaneous (20%) LE
- May be more prevalent in CLE*

- Certain alleles of STAT4 correlate with ↓ oral ulcers**

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%)

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

- Sites: buccal > palate > vermilion (lower lip)
• 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
• May be premalignant – ulcerative / asymmetric lesions suspicious
Case

73 year old female; 3 yr painful upper and lower lip erosions; 5 lb weight loss

No intraoral or genital involvement :
PMH: Sjogren’s syndrome; pernicious anemia; RA
Evaluation

• Swab culture: *Candida parapsilosis*
• Negative/normal
  • Desmogleins
  • Bullous pemphigoid antigens
  • HSV / VZV
• Positives
  • ANA
  • Anti-Ro and -La antibodies
DX: Lupus
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
Ulcers in SLE

- Do not necessarily correlate with systemic disease activity.
- New onset or sudden worsening may be the earliest manifestation of systemic disease.
- Pediatric patients with discoid LE and mucosal involvement more likely to progress to SLE.

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

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
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
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
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”)

• Xerostomia
  • Dry-appearing mucosa
  • Lack of floor of mouth pooling
- Glossitis
- Stringy, thick or ropey saliva
- Food debris in mouth
- Tongue blade sticks
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
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
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
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
Case #5:
62 yo female

10 yr hx of RSD after MVA – narcotic dependent
1 yr hx of painful oral ulcers
The most likely diagnosis is:

- Lichen planus
- SCC
- Pemphigus
- Cicatricial pemphigoid
- None of the above
Rx: dexamethasone swish and spit; PO prednisone; antifungals

- Referred to MC
- “empty sellar syndrome”

- Profound salivary hypofunction
Additional work-up

- AM cortisol: 1.5 (7 – 25)
  - Corticotropin: <5 (10 – 60)
  - Synthetic glucocorticosteroids:
    - Dexamethasone: 0.67 (<0.10)
- A1C: 6.9
- Culture:
  - Candida +
  - HSV 1 +
- Biopsy
  - Ulcer with mixed stromal inflammation
  - DIF -
Case: “Putting it all together”

• Spit matters - dry mouth is like an engine without oil

• Topical steroids – you can have too much of a good thing

• Culture

• HSV likes keratinized surfaces (palate; dorsal tongue; lip)

• Think multifactorial
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
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
Sodium bicarbonate mouth rinse

- Half teaspoon bicarb in glass of water BID
- Helps control infection
- Analgesic (due to its buffer action)
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)
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)
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 xerophthalmia
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
Test Q1:
This pt has chronic oGVHD
1. Her risk of developing SCC is equivalent to erosive OLP

2. Topical calcineurin inhibitors are contraindicated d/t risk of SCC

3. PUVA would be the best treatment

4. Dexamethasone solution would be an appropriate treatment

5. A steroid gel would be poorly tolerated
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2. Topical calcineurin inhibitors are contraindicated d/t risk of SCC

3. PUVA would be the best treatment

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5. A steroid gel would be poorly tolerated
Test Q2:
This pt is 4 mo S/P HSCT.
Best Rx for these lesions is:

• Reassurance
• Increased systemic immunosuppression
• Topical Lidex gel
• Topical Protopic 0.1%
• PO acyclovir
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