Oral Chronic Graft-versus-Host Disease

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Oral cGVHD is **very** common

Oral chronic graft-versus-host disease

- Prominent site of cGVHD
- Wide range of signs/symptoms
- Lichenoid inflammation
- Dry mouth, cavities
- Oral cancer risk
Oral cGVHD features

• Resembles immune/autoimmune conditions
  – lichen planus
  – Sjögren syndrome
  – scleroderma

• Frequently refractory to systemic therapy
  – important role for ancillary care
<table>
<thead>
<tr>
<th>Oral mucosal cGVHD</th>
<th>Salivary gland cGVHD</th>
<th>Sclerotic cGVHD</th>
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</thead>
<tbody>
<tr>
<td><strong>Signs</strong></td>
<td><strong>Symptoms</strong></td>
<td><strong>Signs</strong></td>
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<tr>
<td>Lichen-type features*</td>
<td>Sensitivity to foods/drinks</td>
<td>Thickened, sticky, ropey or foamy saliva</td>
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<tr>
<td>Hyperkeratotic plaques*</td>
<td>Spicy/seasoned foods</td>
<td>Lack of saliva/absence of floor of mouth pooling</td>
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<tr>
<td>Erythema/atrophy†</td>
<td>Acidic foods (citrus, salad dressing, carbonated drinks)</td>
<td>Atrophic mucosa</td>
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<td>Ulcerations with pseudomembranes†</td>
<td>Alcoholic beverages and alcohol containing mouth rinses</td>
<td>Dental caries (interproximal and at the cervical margins)</td>
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<tr>
<td>Atrophic glossitis</td>
<td>Salty foods</td>
<td>Oropharyngeal candidiasis</td>
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<td>Superficial mucoceles†</td>
<td>Hard/crunchy/crusty foods</td>
<td>Frequent water sipping</td>
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<td>Warm (temperature) foods/drinks</td>
<td>Tongue “clicking” while speaking</td>
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<td>Food debris inside the mouth</td>
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<td>Inability to eat dry foods without fluids</td>
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</table>

*Consensus criteria diagnostic features.
†Distinctive (supportive but nondiagnostic) features.
Management of mucosal cGVHD

- High potency topical corticosteroids
  - clobetasol 0.05% gel
  - fluocinonide 0.05% gel
  - dexamethasone 0.5 mg/5 mL (5 min swish/spit)
  - clobetasol 0.05% solution (compound)

- Topical tacrolimus
  - Protopic 0.1% ointment (lips)
  - tacrolimus 0.5 mg/5 mL (compound)

- Combination therapy
Common infectious complications

• Yeast infection
  – contributing factors
    • topical steroid therapy
    • immunosuppression
    • dry mouth
  – management

• Herpes simplex virus
  – immunosuppression
  – “breakthrough” infections
  – acyclovir/valacyclovir
Salivary gland cGVHD

- Functions of saliva
  - lubrication/mastication
  - antimicrobial
  - buffering/remineralization
- Quantitative/Qualitative changes
  - xerostomia/pain/discomfort
  - difficulty eating/swallowing
  - dental caries
    - cervical, interproximal
  - recurrent candidiasis

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>The Major Functions of Saliva</th>
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<tbody>
<tr>
<td>Functions</td>
<td>Salivary Components Involved</td>
</tr>
<tr>
<td>(1) Protective functions</td>
<td></td>
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<tr>
<td>Lubrication</td>
<td>Mucins, proline-rich glycoproteins, water</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Amylase, complement, defensins, lysozyme, lactoferrin, lactoperoxidase, mucins, cystatins, histatins, proline-rich glycoproteins, secretory IgA, secretory leukocyte protease inhibitor, statherin, thrombopelmin</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), insulin-like growth factor (IGF-I &amp; IGF-II), nerve growth factor (NGF)</td>
</tr>
<tr>
<td>Mucosal integrity</td>
<td>Mucins, electrolytes, water</td>
</tr>
<tr>
<td>Lavage/cleansing</td>
<td>Water</td>
</tr>
<tr>
<td>Buffering</td>
<td>Bicarbonate, phosphate ions, proteins</td>
</tr>
<tr>
<td>Remineralization</td>
<td>Calcium, phosphate, statherin, anionic proline-rich proteins</td>
</tr>
<tr>
<td>(2) Food- and speech-related functions</td>
<td></td>
</tr>
<tr>
<td>Food preparation</td>
<td>Water, mucins</td>
</tr>
<tr>
<td>Digestion</td>
<td>Amylases, lipase, ribonuclease, proteases, water, mucins</td>
</tr>
<tr>
<td>Taste</td>
<td>Water, guslin</td>
</tr>
<tr>
<td>Speech</td>
<td>Water, mucins</td>
</tr>
</tbody>
</table>

Adapted from FDI Working Group 10, Core (1992), and Fox (1989).

16 months post allogeneic transplantation
Management of salivary cGVHD

- Saliva substitutes, stimulants, sialogogue therapy
- Caries prevention
  - brushing/flossing/diet
  - fluoride
    - trays w/ 1.1%/0.4%
    - varnish
  - remineralizing agents
- Routine dental visits
  - bitewing radiographs
  - caries control
- Recurrent candidiasis

Figure 15. Intaoral bitewing radiograph demonstrating multiple interproximal dental caries (radiolucencies) in a patient with salivary gland chronic GVHD.
Risk of second cancers

Fig. 1 Scheme of time course and relative risk of second malignancies after allogeneic stem cell transplantation.

Oral cGVHD Summary

• Common, may be initial site of cGVHD
• Wide range of signs/symptoms
• Management
  – topical corticosteroids & tacrolimus
  – avoid irritating food/drink/toothpaste
  – salivary stimulants & moisturizing agents, sialogogues, fluoride, mild/child’s toothpaste
• Routine dental visits with radiographs
• Oral cancer surveillance
• May require treatment for many years
Common Oral cGVHD Prescriptions

**Mucosal cGVHD**
- **Rinses**
  - Best for generalized/extensive involvement
  - 5 minutes, 2-4x/day
  - Dexamethasone 0.1 mg/mL solution
  - Tacrolimus 0.1 mg/mL solution (must be compounded)
- **Gels**
  - Good for limited involvement
  - Dry affected area, can apply with gauze
  - Fluocinonide 0.05% gel
  - Clobetasol 0.05% gel

**Salivary Gland cGVHD**
- **Stimulants & Moisturizing Agents**
  - Biotene mouthwash/gel
  - Sugar-free candy/gum
- **Prescription stimulants**
  - Pilocarpine 5 mg 3x/day
  - Cevimeline 30 mg 3x/day
- **Fluoride (caries prevention)**
  - Prevident 5000
  - Apply nightly (brush on or in custom trays)
- **Remineralization**
  - GC MI Paste Plus
<table>
<thead>
<tr>
<th>Late complication</th>
<th>Prevention</th>
<th>Screening</th>
<th>Management</th>
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<tr>
<td>Oral squamous cell carcinoma</td>
<td>Smoking cessation</td>
<td>Annual clinical examination</td>
<td>Referral to multidisciplinary head and neck oncology center</td>
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<td>Moderate alcohol consumption</td>
<td>Biopsy of atypical/suspicious lesions</td>
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<tr>
<td>Rampant dental caries</td>
<td>Minimize intake of refined carbohydrates (especially sugar-containing soft drinks)</td>
<td>Increased risk in patients with significant salivary gland cGVHD</td>
<td>Treat dental caries as soon as diagnosed</td>
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<tr>
<td></td>
<td>Brush at least twice daily, after eating when possible</td>
<td>Increased risk in patients with orofacial sclerotic cGVHD</td>
<td>Careful follow-up for new or recurrent caries</td>
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<td>Floss daily</td>
<td>Increased risk in patients were severe mucosal disease and avoidance of oral hygiene</td>
<td>Reinforce oral hygiene and dietary habits</td>
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<td></td>
<td>Fluoride 1.1% gel paint on or in custom trays, daily</td>
<td>Examine teeth for evidence of cervical demineralization/decay</td>
<td>Reinforce daily preventive measures</td>
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<td></td>
<td>Remineralizing agent, apply with fluoride</td>
<td>Twice annual dental visits</td>
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<td></td>
<td>Professional fluoride varnish application</td>
<td>• Soft and hard tissue examination</td>
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<td></td>
<td></td>
<td>• Bitewing radiographs (annual)</td>
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<td>Fibrosis</td>
<td>No known preventive measures</td>
<td>Ask patient if aware of tightness/limited opening</td>
<td>Physical therapy</td>
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<td>Extensive sclerotic skin disease, especially with neck involved</td>
<td>Intralesional steroid therapy</td>
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<td>Examine for intraoral buccal fibrotic bands by palpation</td>
<td>Surgery</td>
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<td>Systemic therapy for systemic involvement</td>
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