Multidisciplinary Management of Chronic GVHD: The Oral Cavity

Jacqueline W. Mays, DDS, MHSc, PhD
March 1, 2019
American Academy of Dermatology Annual Meeting
DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Jacqueline W. Mays, DDS, MHSc, PhD
F014- Multidisciplinary Management of Chronic GVHD

DISCLOSURES
I do not have any relevant relationships with industry.
1. Oral cGVHD
2. Diagnosis of oral cGVHD
3. How to differentiate oral GVHD from mimickers
4. Therapy for oral cGVHD
Timing of Oral Post-Transplant Complications

Early
<100 Days Post-Transplant

- Mucositis
- Dry Mouth
- Oral Thrush

Overlap

- Drug-induced complications (MTX, sirolimus)
- Viral infections (HSV, HPV)

Late
>100 Days Post-Transplant

- cGVHD
  - Dry Mouth
  - Perioral Fibrosis
  - Oral ulcers
  - Lichenoid lesions
  - Hyperkeratosis
- Secondary oral cancer: squamous cell; HPV
Oral Chronic Graft-versus-Host Disease (cGVHD)

- Ulceration
- Hyperkeratosis
- Salivary gland dysfunction
- Lichenoid lesion
- Lichenoid hyperkeratosis
- Sclerosis
Salivary Glands are a target of cGVHD

→ Decreased saliva secretion
→ Dental caries
→ Periodontal atrophy/disease
→ Oral mucosal fragility
1. LYMPHOCYTIC INFILTRATE
2. ALTERED EPITHELIUM
3. EPITHELIAL CLEFTING
Incidence of Oral cGVHD

• Over 8800 patients underwent allogeneic HSCT in 2016, an increase of 6% since 2013 (United States data)\(^1\)

• \(~50\%) of allogeneic HSCT patients develop cGVHD, an autoimmune-like disease
  – Multi-system
  – Acute and chronic forms
  – Begins with donor cell recognition of recipient tissues as foreign
  – Inflammatory and fibrotic components of disease

• Of those patients with cGVHD, \(40\text{-}83\%)\ have oral manifestations

---

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report

Oral cGVHD Diagnostic Criteria

1) Sufficient for diagnosis: Lichen planus-like changes

2) - or -

   The presence of at least 1 distinctive manifestation (xerostomia, mucoceles, mucosal atrophy, pseudomembranes, ulcerations) confirmed by pertinent biopsy or other relevant tests

3) The exclusion of other possible diagnoses
   • Oral infections
   • Drug reaction
   • New cancers
### Oral cGVHD Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnostic Features of cGVHD</th>
<th>Distinctive Features of cGVHD</th>
<th>Other Features of cGVHD</th>
<th>Common Findings in GVHD</th>
<th>Histopathologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lichen planus-like changes</td>
<td>• Xerostomia</td>
<td>• Foamy or thick saliva</td>
<td>• Gingivitis</td>
<td>Mucosa</td>
</tr>
<tr>
<td></td>
<td>• Mucoceles</td>
<td>• Atrophic glossitis</td>
<td>• Mucositis</td>
<td>Lymphocyte infiltration at the lichenoid interface</td>
</tr>
<tr>
<td></td>
<td>• Mucosal atrophy</td>
<td>• Difficulty chewing and swallowing food without water</td>
<td>• Erythema</td>
<td>infiltration of mucosa (exocytosis)</td>
</tr>
<tr>
<td></td>
<td>• Ulcers</td>
<td>• Oral mucosal sensitivity to foods that are spicy/salty/acidic/minty/crunchy</td>
<td>• Pain</td>
<td>variable apoptosis</td>
</tr>
<tr>
<td></td>
<td>• Pseudomembranes</td>
<td>• New-onset taste changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salivary Gland</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Periductal lymphocytic infiltrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• damaged intralobular ducts or acinar tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• fibroplasia in periductal stroma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mixed lymphocytic and plasmacytic inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Features of Oral cGVHD: Lichenoid Lesion
Distinctive Features of Oral cGVHD: Palate

- Palatal hyperkeratosis
- Mucoceles
- Erythema
Distinctive Features of Oral cGVHD: Tongue

A. Atrophic glossitis
B. Hyperkeratosis with patchy atrophy and associated erythema
C. Patchy tufted hyperkeratosis
Distinctive Features of Oral cGVHD: Pseudomembranous Ulcerations
The Importance of Oral Health in Comprehensive Health Care

THE CONCISE ORAL EXAM
Complication: Herpes Simplex Virus Recrudescence

HSV reactivation is common: acute onset, exquisitely painful oral ulcers
Diagnosis: swab ulcer for PCR lab test for HSV DNA

Management: lidobenalox, systemic antivirals (switch agent or increase dose)
Complication: mTOR inhibitor/Sirolimus-Induced Oral Stomatitis

Excess circulating levels of mTOR (Mammalian target of rapamycin) inhibitors such as sirolimus may induce painful aphthous-like ulcers with well-demarcated borders and focal erythema.

Management: topical steroids, lidobenalox, adjustment of sirolimus dose
Clinical Presentation Matters!

- Different types of oral cGVHD may need different treatment
- The underlying pathology is different
- The prognosis is different

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report

Madan H. Jagasia 1, Hildegard T. Greinix 2, Mukta Arora 3, Kirsten M. Williams 4,5, Daniel Wolff 6, Edward W. Cowen 4, Jeanne Palmer 7, Daniel Weisdorf 3, Nathaniel S. Treister 8, Guang-Shing Cheng 9, Holly Kerr 10, Pamela Stratton 11, Rafael F. Duarte 12, George B. McDonald 9, Yoshihiro Inamoto 13, Afonso Vigorito 14, Sally Arai 15, Manuel B. Datiles 16, David Jacobsohn 5, Theo Heller 17, Carrie L. Kitko 18, Sandra A. Mitchell 19, Paul J. Martin 9, Howard Shulman 9, Roy S. Wu 20, Corey S. Cutler 21, Georgia B. Vogelsang 22, Stephanie J. Lee 9, Steven Z. Pavletic 4, Mary E.D. Flowers 9,*
## Diagnosis and Staging: NIH Global Severity of cGVHD

<table>
<thead>
<tr>
<th>MOUTH</th>
<th>No symptoms</th>
<th>Mild symptoms with disease signs but not limiting oral intake significantly</th>
<th>Moderate symptoms with disease signs with partial limitation of oral intake</th>
<th>Severe symptoms with disease signs on examination with major limitation of oral intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus-like features present:</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The eGVHD App has the potential to improve the accuracy of graft versus host disease assessment: a multicenter randomized controlled trial.

Schoemans HM^1^, Goris K^2^, Van Durm R^3^, Fieuvx S^4^, De Geest S^5^, Pavletic S^6^, Im A^7^, Wolff D^8^, Lee SJ^9^, Greix G^10^, Duarte RF^11^, Poiré X^12^, Selleslag D^13^, Lewalle P^14^, Kerre E^15^, Graux C^16^, Baron F^17^, Maertens JA^2^, Dobbels F^18^; EBMT Transplantation Complications Working Party
Report


Stephanie J. Lee 1, Daniel Wolff 2, Carrie Kitko 3, John Koreth 4, Yoshihiro Inamoto 5, Madan Jagasia 6, Joseph Pidala 7, Attilio Olivieri 8, Paul J. Martin 1, Donna Przepiorka 9, Iskra Pusic 10, Fiona Dignan 11, Sandra A. Mitchell 12, Anita Lawitschka 13, David Jacobsohn 14, Anne M. Hall 1, Mary E.D. Flowers 1, Kirk R. Schultz 15, Georgia Vogelsang 16, Steven Pavletic 12,*
Measuring Response to Treatment: Form A

<table>
<thead>
<tr>
<th>Mucosal Changes</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild erythema or moderate erythema (&lt;25%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate (≥25%) or Severe erythema (&lt;25%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe erythema (≥25%)</td>
<td>3</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lichen-like changes (&lt;25%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Lichen-like changes (25-50%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lichen-like changes (&gt;50%)</td>
<td>3</td>
</tr>
<tr>
<td>Ulcers</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Ulcers involving (≤20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe ulcerations (&gt;20%)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td><strong>for all mucosal changes</strong></td>
<td><strong>8</strong></td>
</tr>
<tr>
<td>Mouth</td>
<td>None</td>
<td>Mild erythema or moderate erythema (&lt;25%)</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Ulcers</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Erythema**: None (0), Mild erythema or moderate erythema (<25%) (1), Moderate (≥25%) or Severe erythema (<25%) (2), Severe erythema (≥25%) (3)
- **Lichenoid**: None (0), Lichen-like changes (<25%) (1), Lichen-like changes (25-50%) (2), Lichen-like changes (>50%) (3)
- **Ulcers**: None (0), Ulcers involving (≥20%) (3), Severe ulcerations (>20%) (6)

Total score for all mucosal changes = 3
<table>
<thead>
<tr>
<th>Mouth</th>
<th>None</th>
<th>0</th>
<th>Mild erythema or moderate erythema (&lt;25%)</th>
<th>1</th>
<th>Moderate (&lt;25%) or Severe erythema (&lt;25%)</th>
<th>2</th>
<th>Severe erythema (≥25%)</th>
<th>3</th>
<th>Total score for all mucosal changes</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>None</td>
<td>0</td>
<td></td>
<td>1</td>
<td>Moderate (&lt;25%) or Severe erythema (&lt;25%)</td>
<td>2</td>
<td>Severe erythema (≥25%)</td>
<td>3</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>None</td>
<td>0</td>
<td>Lichen-like changes (&lt;25%)</td>
<td>1</td>
<td>Lichen-like changes (25-50%)</td>
<td>2</td>
<td>Lichen-like changes (&gt;50%)</td>
<td>3</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Ulcers</td>
<td>None</td>
<td>0</td>
<td>Ulcers involving (&lt;20%)</td>
<td>3</td>
<td>Severe ulcerations (≥20%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
## Topical Therapy for Oral cGVHD Has Limited Efficacy

| Oral | Acute GVHD | Mucositis |  • Cryotherapy  
|      |            | Supersaturated calcium phosphate rinses |  • Pain control (opioid analgesics)  
|      | Lichen planus-like changes |  • Steroid rinses (starting with World Health Organization Class VII low potency agents and moving up in strength)  
|      |            |  • Calcineurin-inhibitor rinses |  
| Chronic GVHD | Oral ulcers (isolated) |  • Topical steroid gel (starting with World Health Organization Class V moderate potency agents and moving up in strength)  
|      |            |  • Tacrolimus gel  
|      |            |  • Intra-lesional triamcinolone injection |  
| chronic | Xerostomia |  • Oral lubricants  
|      |            |  • Salivary stimulants (sugar-free gum/lozenges) |  • Cholinergic agonists (pilocarpine, cevimeline)  
|      | Reduced oral aperture (sclerosis) |  • Progressive stretching regimen  
|      |            |  • Peri-oral steroid injections  
|      |            |  • Surgical intervention |  
|      | Preventive Measures |  • Stringent oral/dental hygiene  
|      |            |  • Routine dental cleaning with possible endocarditis prophylaxis  
|      |            |  • Surveillance for infection and malignancy |  

- First Line: Dexamethasone oral suspension (0.1mg/ml) - Expected ~29-58% patient response rate<sup>1-2</sup>

- Second Line: Not well established


Post-Transplant patients should return to regular dental care ASAP

Figure 3. Percentage change in the number of caries and extractions from before alloHCT to after alloHCT.

Post-Transplant Oral Care

- Early post-transplant: Emergency care only for dental infections
- Oral Hygiene Instruction: twice a day tooth brushing with a fluoride based toothpaste
- Use an extra soft-bristle toothbrush that is replaced frequently for basic oral hygiene
- Electric toothbrush may aid patients with reduced joint mobility.
- Sodium fluoride oral rinse (ACT fluoride rinse) after brushing for caries prevention
- Oral balance gel may be used before bed and as needed for dry mouth (Biotene, other oral lubricants available)
- Provide with petrolatum hydrophilic topical ointment for dry lips as needed
Thank you!