Oral & Vulvovaginal GVHD

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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S001 Advanced Medical Dermatology

DISCLOSURES
I do not have any relevant relationships with industry.
Case

- Pt referred to vulvar clinic for management of lichen sclerosus
- PMH: Hx of AML s/p stem cell transplant
- Also complains about sores in her mouth
- Skin rash
Pathology

Skin

Vulva

Photos courtesy of Tim McCalmont MD. San Francisco, CA
Chronic GVHD: Mucosal sites

- 60-70% of patients who receive allo transplant manifest GVHD\(^1\)
- Skin is most common organ system involved (~75% of patients)\(^2\)
  - oral mucosa (45– 83%)
  - liver, eye, GI tract, lung, female genital tract and joints
- Incidence of female genital cGVHD varies from 19-52%\(^3\)
- Male genital disease less well documented ~ 12% of patients\(^4\)

NIH consensus criteria:
Diagnostic and Distinctive signs

• The diagnosis of cGVHD requires:
  • Exclusion of acute GVHD
  • Presence of at least 1 diagnostic clinical sign of cGVHD OR presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests
  • Exclusion of other possible diagnoses

• Manifestations common to both acute and chronic GVHD
  • gingivitis, mucositis, erythema, and pain
Oral Disease: Diagnostic signs

• Lichen planus-like lesion
Distinctive features: Oral GVHD

• Mucoceles
  • Occur when ductal openings of the minor salivary glands are blocked → lymphocytic infiltrate in the underlying skin or salivary glands.
  • Typically painless, may be bothersome

• Xerostomia

• Mucosal Atrophy
Distinctive Signs: Oral GVHD

- Oral ulcerations & pseudomembranes
  - occur at any site on the oral mucosa, including the roof of the mouth, buccal mucosa, tongue, gingiva, vestibules, and lips
Other signs & symptoms

- Sclerosus
  - May lead to narrowing of oral aperture
- Tooth decay

- Symptoms
  - Pain
  - Taste impairment
  - Oral sensitivity
  - Dryness
  - Decreased range of motion
Oral GVHD DDX

Irradiation xerostomia

Drug
- mTor inhibitors
- calcineurin inhibitors

Infection
- HSV
- HPV
- Candida
  - Removed by gentle scraping
  - KOH

Secondary malignancy
Treatment
NIH Ancillary and supportive care working group 2014

• Topical steroids in gel formulation
• Dexamethasone swish and spit
  • 0.1 mg/mL (0.01%) 10 mL x3-6/d
• Topical tacrolimus ointment
• Tacrolimus (oral solution compounded)
  • 0.1mg/mL (0.01% 5 mL x3/d)
• Intraleisonal Kenalog
• Dental trays may increase effectiveness for gingival involvement
• Systemic therapies
  • multidisciplinary approach with heme/onc
Supportive care

- Routine dental care/cleanings Q 6 months
  - For patient prone to caries consider chlorhexidine mouth wash for limited time (taste loss and tooth discoloration)
- Pain management
  - Viscous Lidocaine (2% solution) individually, or mixed with Kaolin/Pectin or aluminium hydroxide - magnesium hydroxide (Maalox) and diphenhydramine (1:1:1) Patients may swish with 5 mL for 5 minutes and spit.
  - Not more than 5 times daily to limit lidocaine systemic absorption.
- Dry mouth
  - Biotene oral balance gel, Stoppers 4 Dry Mouth Spray, Oasis, Salivart, Xerolube
  - Sialogogues
- Gentle oral care
  - bland toothpaste (No mint or cinammon)
  - alcohol free mouthwashes (Closys)
- Physical therapy for sclerosus
- Cancer screening annually
  - Increased risk of oral SCC
  - Biopsy atypical or persisting lesions
Female genital GVHD

- Likely under-recognized and often diagnosed too late
- Look, don’t just ask
- Better prognosis if caught early
- Significant QOL impairment
Incidence Female Genital GVHD
61 patients

- 49% of women developed genital GVHD
- Median time of onset 10 months
- 7 cases occurred beyond 12 months
- Patients with genital disease were more likely to have extensive cGVHD

GVHD sites and Their Association with Genital Disease

- 23 (72%) of patients had cGVHD in other organs
- 4 patients with severe genital cGVHD had no other mucocutaneous manifestations

<table>
<thead>
<tr>
<th>Chronic cGVHD organ sites</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Eyes</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Skin</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Lungs</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Gut</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6)</td>
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</tbody>
</table>

Symptoms of Genital GVHD

- Dryness
- Burning
- Itching
- Pain
- Dyspareunia
  - Introital pain
- Amenorrhea/cyclic pain secondary to hematocolpos

Diagnostic Signs
• Lichen planus- like
• Lichen sclerosus- like
• Labial or clitoral agglutination or vaginal scarring

Distinctive signs
• Fissures, erosions, ulcers
<table>
<thead>
<tr>
<th>DDX</th>
<th>Vaginal dryness</th>
<th>Erosions/Ulcers</th>
<th>Mucosal Erythema</th>
<th>White plaques and patches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estrogen deficiency</td>
<td>Viral infection</td>
<td>Estrogen deficiency</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>Drug</td>
<td>Drug</td>
<td>Secondary malignancy</td>
<td>Erythematous candidiasis</td>
<td>Lichen sclerosus</td>
</tr>
<tr>
<td></td>
<td>Candidiasis</td>
<td>Bacterial infection</td>
<td>Lichen simplex chronicus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexually transmitted infections (STI)</td>
<td>Irritant or allergic contact dermatitis</td>
<td>Post-inflammatory pigment alteration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial infection</td>
<td>Vulvar intraepithelial neoplasia (VIN)</td>
<td>Candidiasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunobullous disease</td>
<td>Plasma cell mucositis</td>
<td>Condyloma</td>
<td></td>
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</tbody>
</table>

Dysplasia Risk

• Cervical cancer 13x higher among pts s/p Allo-HSCT
• Genital HPV infection ~ 40% at 20 years. Most often in 1\textsuperscript{st} 5 years
• Persistent, multifocal or severe genital HPV disease in 13–17%
• cGVHD is an independent risk factor for dysplasia
  • Likely due to viral re-activation and compromised cell mediated immunity
• Annual Pap screening
• ? Role of HPV vaccine
Treatment

• Correction of estrogen deficiency
  • Topical/intravaginal estrogen if not contraindication

• Topical and intravaginal steroids
  • High potency topical steroid, tapered and continued at maintenance dose
  • No commercially available intravaginal preparations
    • Hydrocortisone 25mg rectal suppositories
    • Hydrocortisone 10% foam or compounded 3-5g for 2 weeks then taper
    • Vaginal application results in systemic absorption
    • Place pea size of steroid ointment on dilator

• Topical and intravaginal tacrolimus
  • Suppository 2mg per 2 g suppository compounded

• Dilator therapy

• Systemic therapy

• Surgical intervention for lysis or adhesions or vaginal reconstruction
Surveillance and Supportive Measures

• Educate patients about signs and sx of genital GVHD
• Intermittent dilator use for non-sexually active patients
• Surveillance for infection, secondary malignancy
• Genital exam (including vaginal exam) 3-6 months after transplant or sooner pending symptoms
• If flaring: rule out infection/contact dermatitis/dysplasia
• Daily emollient
• Non-irritating personal lubricant
  • Slippery stuff extra gentle lubricant
Male Genital GVHD

Diagnostic signs:
• phimosis or urethral meatus scarring

Genital Chronic GVHD in Men after Hematopoietic Stem Cell Transplantation: A Single-Center Cross-Sectional Analysis of 155 Patients

<table>
<thead>
<tr>
<th>Genital changes</th>
<th></th>
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<tbody>
<tr>
<td>Absent</td>
<td>124 (80%)</td>
</tr>
<tr>
<td>Present</td>
<td>31 (20%)</td>
</tr>
<tr>
<td>Noninflammatory genital skin changes</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Melanotic macules on the glans penis</td>
<td>3</td>
</tr>
<tr>
<td>Postinflammatory hyperpigmentation of the glans</td>
<td>2</td>
</tr>
<tr>
<td>Unspecific acute irritative balanitis</td>
<td>2</td>
</tr>
<tr>
<td>Penis deviation during erection (not objectified)</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory genital skin changes, possible GVHD</td>
<td><strong>21 (13%)</strong></td>
</tr>
<tr>
<td>Balanoposthitis</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Lichen sclerosis–like</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Phimosis</td>
<td>5 (3%)</td>
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Final thoughts

• Mucosal GVHD is common
• Must examine genitals, not just ask
• Often requires systemic therapy and multidisciplinary care
• Monitor for infection and secondary cancer
• Biopsy and re-biopsy if necessary (always include hx of transplant in report)

  • Look at supplemental material
Thank you

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