Graft-versus-Host Disease of the Gastrointestinal Tract and Liver

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Introduction

• What is GVHD?
• What are possible causes?
• How is it classified?
• How it may present?
• How to treat?

Hematopoietic Stem Cell Transplant is an Immunotherapy Treatment

• Disease
• Donor
• Prior treatment
• Conditioning
• Comorbidities

• Relapse
• GVHD
• Infection
• Mortality

Immune System
GVHD and Graft-versus-Leukemia Effect (GVL)

Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

Horowitz et al; Blood 1990

Graft-versus-Host-Disease

• Immune reaction triggered when non-self cells (donor) react toward self-cell (recipient) recognizing them as foreign

• Immunosuppressive medications are used to prevent this reaction while donor cells develop tolerance toward foreign cells
Factors Contributing to GVHD

- Non-identical graft (HLA or Gender)
- GVHD prevention regimen
- Conditioning regimen intensity
- Source of stem cells (peripheral blood vs bone marrow)
- Microbiome

Incidence of Acute GVHD

Acute GVHD Grade B-D (sibling donor)
Median 39%

Acute GVHD Grade B-D (Unrelated donor)
Median 59%

Jagasia et al; BBMT 2015
Incidence of Late Acute GVHD and Chronic GVHD

**Late acute GVHD**

- Cumulative incidence over months after HCT.
- 10% incidence.

**Chronic GVHD**

- Cumulative incidence over months after HCT.
- 47% incidence.

GVHD Prevention

- Tacrolimus, Methotrexate
- Post-transplant Cyclophosphamide, Tacrolimus, Mycophenolate
- Tacrolimus, Sirolimus
- Post transplant Cyclophosphamide, Sirolimus, Mycophenolate
- Tacrolimus, mycophenolate
- T cell manipulation (e.g. Orca graft)
- Clinical trials (e.g. Microbiota modification trials)
Acute or Chronic GVHD?

- **Timing**
  - Less then 100 days (acute) and more then 100 days (chronic)
  - Overlap
- **Pathology**
  - Acute: destruction as result of inflammatory T cells processes
  - Chronic: tissue injury with abnormal repair leading to fibrosis, scarring
- **Organs affected**
  - Acute: Skin, gastrointestinal, Liver
  - Chronic: Eyes, gastrointestinal, skin, joints, muscles, lungs, liver, kidneys, nervous system, serosal cavities, genitalia

[Image of the digestive system]

https://www.niddk.nih.gov/health-information/digestive-diseases/digestive-system-how-it-works
Symptoms of GVHD

- Mouth (chronic): Oral dryness, ulceration, pain, gum bleeding
- Esophagus (chronic): Difficulty swallowing, painful swallowing, choking
- Stomach (acute/chronic): abdominal pain, weight loss, loss of appetite
- Small and large bowel (acute/chronic) loss of appetite, abdominal pain, weight loss, diarrhea, bleeding, constipation
- Liver: no symptoms but elevated liver enzymes (Bilirubin, AST, ALT)

GVHD in Mouth

- Oral dryness
- Ulcerations
- Pain/Irritation
- Gum bleeding
- Tooth decay
GVHD in Esophagus

- **Symptoms**
  - Difficulty swallowing (Dysphagia)
  - Painful swallowing (Odynophagia)
  - Choking
- **Diagnostic Terms**
  - Schatzki ring
  - Esophageal stricture or stenosis
- **Caused by**
  - chronic scarring of muscles
- **Diagnosis**
  - Clinical presentation
  - Endoscopic gastroduodenoscopy
  - Barium Swallow study

Endoscopic gastroduodenoscopy
Management

Combination of immunosuppressive therapy and endoscopic intervention

https://www.ajronline.org/doi/pdf/10.2214/ajr.142.3.50

Endoscopic dilatation

GVHD in Stomach

- Symptoms
  - abdominal pain
  - weight loss
  - loss of appetite
- Present in both acute and chronic GVHD

- Diagnosis
  - Endoscopic gastroduodenoscopy

- Management
  - Topical corticosteroids
  - Systemic immunosuppressive therapy

Gastroparesis – Delayed Gastric Emptying

- Movement of food from stomach to small intestine is stopped or delayed
- Symptoms: inability to eat, feeling full after eating only a little food
- Gastric emptying scan can help with diagnosis
- Treatment
  - Immunosuppression
  - Gut motility agent
  - Proton pump inhibitor
Symptoms of GVHD in Small and Large Bowel

- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Blood in stool
- Weight loss

Infectious Causes of Diarrhea

- Bacterial: (Clostridium difficile, campylobacter, Shigella)
- Viral: (CMV, Adenovirus, EBV, Rotavirus, norovirus)
- Cryptosporidium
- Mycobacterium
Other Causes of Diarrhea

- Inflammatory bowel disease
  - Crohn’s disease, Ulcerative colitis
- Cord colitis syndrome
- Thrombotic microangiopathy syndrome
- Disease involvement of gastrointestinal system
- Pancreatic insufficiency
- Small bowel intestinal bacterial overgrowth
- Medications:
  - mycophenolate, antibiotics, conditioning chemotherapy

Management of Diarrhea Caused by GVHD

- Diagnosis
  - Clinical work up
  - Flexible Sigmoidoscopy
  - Colonoscopy
- Treatment
  - Immunosuppressive therapy
Liver GVHD

• Symptoms:
  • Jaundice
  • Sometimes no symptoms
• Can occur in both acute and chronic GVHD
• Usually, there are also other organs with GVHD

Other Causes of Abnormal Liver Enzymes

• Medications
• Venooclusive disease
• Fatty Liver disease
• Iron overload
• Infections (Hepatitis, CMV, Adenovirus)
• Gall bladder disease
Management of Liver GVHD

• Investigation
  • Ultrasound or CT Abdomen
  • HiDA Scan
  • Transjugular liver biopsy
  • Infectious work up
  • Medication review

• Treatment
  • Immunosuppression

Acute GVHD Grading

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (Bilirubin)</th>
<th>Upper GI</th>
<th>Lower GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rash</td>
<td>&lt; 2.0 mg/dl</td>
<td>No protracted nausea</td>
<td>&lt;500 ml diarrhea</td>
</tr>
<tr>
<td>1</td>
<td>&lt;25% Body surface area</td>
<td>2.0-2.9 mg/dl</td>
<td>Persistent nausea, vomiting or anorexia with histologic changes</td>
<td>&gt;500 diarrhea</td>
</tr>
<tr>
<td>2</td>
<td>25-50% Body surface area</td>
<td>3.1-6.0 mg/dl</td>
<td></td>
<td>&gt;1000 diarrhea</td>
</tr>
<tr>
<td>3</td>
<td>&gt;50% generalized redness and scaling on skin</td>
<td>6.1-15 mg/dl</td>
<td></td>
<td>&gt;1500 diarrhea</td>
</tr>
<tr>
<td>4</td>
<td>Large blisters and/or peeling skin</td>
<td>&gt;15 mg/dl</td>
<td></td>
<td>Severe abdominal pain, poor movement of stool, frank blood in stool</td>
</tr>
</tbody>
</table>
Chronic GVHD Grading

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2 organs or sites (except lung) with score of 1</td>
<td>3 or more organs with score 1</td>
<td>At least 1 organ or site with score 3</td>
</tr>
<tr>
<td>• Mild oral symptoms, no decrease in oral intake</td>
<td>• At least 1 organ site with score 2</td>
<td>• &gt;50% body surface involved</td>
</tr>
<tr>
<td>• Mild dry eyes, lubricant eyedrops ≤ 3X/day</td>
<td>• 19-50% body surface area involved or superficial sclerosis</td>
<td>• Deep sclerosis, impaired mobility or ulceration</td>
</tr>
<tr>
<td></td>
<td>• Moderate dry eyes, eyedrops &gt; 3X/day or punctal plugs</td>
<td>• Severe oral symptoms with major limitation in oral intake</td>
</tr>
<tr>
<td></td>
<td>• Lung score 1 (FEV1 60-79% or dyspnea (shortness of breath) with stairs)</td>
<td>• Severe dry eyes affecting activities of daily living</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lung score 2 (FEV1 40-59% or dyspnea (shortness of breath) walking on flat ground</td>
</tr>
</tbody>
</table>

Lee et al; Blood 2017

Intestinal Microbiota

• Microorganisms in gut
• Play valuable role in promoting patient immune system
• Decrease in diversity and presence of certain microbial species has been shown to be associated with:
  • risk of graft versus host disease
  • failure to respond to treatment
  • non-relapse mortality
• Several clinical trials are undergoing to modulate gut microbiome to prevent and improve treatment responses
Microbiome Clinical Trials – Fecal Transplant

- Fecal microbiota transplant for steroid refractory GVHD\(^1\)
  - Received fresh donor stool suspension through nasoduodenal tube
  - 10 of 15 patients achieved remission
- Third-party fecal microbiota transplantation following allogeneic-HCT reconstitutes microbiome diversity\(^2\)


Other Microbiome Clinical Trials

- **Gluten free diet** in preventing GVHD in patients undergoing HCT
- **Lactobacillus rhamnosus GG** doesn’t reduce incidence of GVHD in patients who have undergone HCT\(^1\)
- **CBM588** in Improving Clinical Outcomes in Patients Who Have Undergone Donor Hematopoietic Stem Cell Transplant
- **Human Lysozyme Goat Milk** for the Prevention of Graft Versus Host Disease in Patients With Blood Cancer Undergoing a Donor Stem Cell Transplant

1. Gorshein et al; Clin transplant 2017
Treatment Options for GVHD

- Corticosteroids
  - Systemic (Oral vs Intravenous)
  - Topical (Budesonide, Beclomethasone)
- Tacrolimus, Sirolimus, Mycophenolate Mofetil (Cellcept®)
- Ruxolitinib (Jakafi®)
- Belumosudil (FDA Breakthrough designation)
- Ibrutinib
- Infliximab, Etanercept
- Extracorporeal photopheresis (ECP)
- Clinical trials

Extracorporeal photopheresis

- Blood is drawn from patient
- Blood is separated.
- Plasma and red blood cells are returned to patient
- White blood cells are photoactivated with UVA radiation
- Photoactivated white blood cells are returned to the patient
Managing GVHD is a Team Effort

• Complex disease and treatment requires:
  • close communication with transplant team
  • patient compliance with treatment plan
• Outcomes improving:
  • better understanding of mechanisms and available treatments
  • better supportive care
• Emotional and social support
• Work with dietitian to overcome nutritional challenges
• Physical rehabilitation
• Multiple drugs
• Multispecialty support