Chronic Graft versus host disease

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St László Hospital, Budapest
Outline

1. Definition, Pathology & Risk factors
2. Diagnosis & Clinical Manifestations
3. Epidemiology
4. Grading & Prognosis
5. Treatment
Definition

- cGVHD is an *immunoregulatory disorder* occurs after allogeneic hematopoietic cell transplantation and shares features of *autoimmunitiy* and *immunodeficiency*

- cGVHD is the *major cause of late non-relapse mortality and morbidity* after allogeneic hematopoietic cell transplantation

- Mortality and morbidity is due to cGVHD and it’s treatment as well
Pathology of cGVHD

- Chronic GVHD is also thought to be *induced by donor T-cells* but the pathophysiology is not well defined.

- Features of cGVHD resemble other autoimmune diseases like
  - Sjogren syndrome,
  - scleroderma and
  - primary biliary cirrhosis
Potential mechanism of chronic graft-versus-host disease (GVHD) induction

Autoreactive T Lymphocytes

CD4+ helper T cells → CD8+ effector T cells

→ IL-10

→ IL-2

→ IFN-γ, IL-2

→ Killing

→ NKG cells

→ Self Recognition

- Tissue Destruction -

→ Tumor cells
Overview of the B-cell functions and their potential role in GVHD.
Major risk factors for the development of chronic GVHD

1. Prior acute GVHD
2. Previous splenectomy
3. Higher degree of HLA mismatch
4. Older age (donor/recipient)
5. Alloimunization of the donor (pregnancy, transfusions)
6. CMV seropositivity (donor/recipient)
7. TBI
8. Female donor to male recipient
9. PBSCT

M Flowers Blood 2011 Mar;117(11)3214-19
Major risk factors for the development of chronic GVHD

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9. PBSCT

M Flowers Blood 2011 Mar;117(11)3214-19
Diagnosis – Distinction between acute and chronic GVHD

Old definition:

SCT

Day 100

Acute GVHD

Chronic GVHD
Diagnosis – Distinction between acute and chronic GVHD

*Old definition:*

- **Acute GVHD**
- **Onset of Chronic GVHD**
  - **Progressive**
  - **Quiescent**
  - **De novo**

**SCT**

**Day 100**
Diagnosis – Distinction between acute and chronic GVHD

Old definition:

- Acute GVHD: Onset of Chronic GVHD
  - Progressive
  - Quiescent
  - De novo

Day 100

3 years
## Diagnosis – Distinction between acute and chronic GVHD

**New definition - NIH consensus**

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI</th>
<th>Presence of acute GVHD features</th>
<th>Presence of chronic GVHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute</td>
<td>≤ 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent or late-onset acute</td>
<td>&gt; 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Diagnosis – Distinction between acute and chronic GVHD

SCT

Day 100

Acute GVHD

Chronic GVHD

Acute GVHD

- classic

- recurrent

- late onset

- persistent

Chronic GVHD

- Progressive

- Quiescent

- De novo
Diagnosis – Distinction between acute and chronic GVHD

Acute GVHD
- Classic

Chronic GVHD
- Progressive
- Quiescent
- De novo

Overlap Syndrome
- Recurrent
- Late onset
- Persistent

Time: Day 100

SCT
Clinical manifestations of chronic GVHD

1. Skin
2. Mouth
3. Eyes
4. Joints, fascia and muscles
5. Liver
6. Gastrointestinal tract
7. Lung
Other possible clinical and laboratory manifestations

- Exocrine pancreatic insufficiency
- Ascites, pericardial or pleural effusions
- Thrombocytopenia, eosinophilia, lymphopenia
- Autoantibodies, IgA deficiency
NIH consensus criteria for diagnosis of chronic GVHD

- Other possible diagnosis must be excluded
- No time limit is set for the diagnosis
- Presence of
  - at least 1 diagnostic clinical sign
  - Or at least 1 distinctive sign confirmed by pertinent biopsy or other relevant test (eg Schirmer)
<table>
<thead>
<tr>
<th>SITE</th>
<th>Diagnostic</th>
<th>Distinctive</th>
<th>Both acute and chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Poikiloderma, Sclerotic features</td>
<td></td>
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</tbody>
</table>
Poikiloderma

Weight loss
Poikiloderma

Weight loss
Poikiloderma with sclerosis
Poikiloderma with sclerosis
Extensive sclerosis
## Signs and symptoms of chronic GVHD

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<tr>
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<td></td>
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<tr>
<td></td>
<td>Sclerotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen, restriction of mouth opening</td>
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Lichen
Restriction of mouth opening from sclerosis
## Signs and symptoms of chronic GVHD

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<td>Muscles fascia, joints</td>
<td>Fasciitis, contractures</td>
<td></td>
</tr>
</tbody>
</table>
Fasciitis with joint stiffness
Fasciitis with joint stiffness
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<td></td>
<td></td>
</tr>
<tr>
<td>GI tract</td>
<td>Esophageal web, Strictures (upper mid third)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Esophagus

stricture

web
## Signs and symptoms of chronic GVHD

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<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchiolitis obliterans</td>
<td>Bronchiolitis obliterans</td>
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Bronchiolitis obliterans
### Signs and symptoms of chronic GVHD

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<tr>
<td>Skin</td>
<td>Poikiloderma, Sclerotic features</td>
<td>Depigmentation</td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen, restriction of mouth opening</td>
<td>Xerostomia</td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td>Keratoconjunctivitis sicca</td>
<td></td>
</tr>
<tr>
<td>Muscles fascia, joints</td>
<td>Fasciitis, contractures</td>
<td>Myositis</td>
<td></td>
</tr>
<tr>
<td>GI tract</td>
<td>Esophageal web, Strictures (upper mid third)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchiolitis oblitereans</td>
<td>Bronchiolitis oblitereans</td>
<td></td>
</tr>
</tbody>
</table>
Depigmentation
<table>
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</thead>
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<tr>
<td>Skin</td>
<td>Poikiloderma, Sclerotic features</td>
<td>Depigmentation</td>
<td>Erythema</td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen, restriction of mouth opening</td>
<td>Xerostomia</td>
<td>Mucosites</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td>Keratoconjunctivitis sicca</td>
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<td></td>
</tr>
<tr>
<td>GI tract</td>
<td>Esophageal web, Strictures (upper mid third)</td>
<td></td>
<td>Anorexia weight loss</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td>Bilirubin SAP ALT AST</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchiolitis obliterans</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Incidence of cGVHD

- 40% HLA identical sibling unmanipulated SCT
- 50% MM related SCT
- 70% MUD SCT

Sullivan K et al Semin Hematol. 1991;28:250-259
Median Onset of cGVHD
Days following SCT

D+201  HLA identical sibling

D+159  MM related donor

D+133  MUD donor

Sullivan K et al Semin Hematol. 1991;28:250-259
Initial presentation of chronic graft-versus-host disease (GVHD) in four cohorts
Other characteristics of cGVHD of 324 pts in FHCRC 2003-2005

- Quiescent onset 60%
- De novo onset 27%
- Progressive onset 13%
- On steroid at diagnosis 34%
- Platelets <100,000 at diagnosis 31%

Outcomes among 743 patients with chronic GVHD transplanted at FHCRC between 1994 and 2000

Time to discontinuation of immunosuppression is prolonged among patients with more sites affected by chronic GVHD.
Grading of chronic GVHD (on 20 pts)

- **Limited disease**
  - Localized skin involvement and/or hepatic dysfunction

- **Extensive disease**
  - Generalized skin involvement
  - Localized skin or hepatic dysfunction + 1 of:
    - Liver histology showing chronic hepatic disease
    - Schirmer test verified involvement of eye
    - Oral mucosal biopsy verified involvement of salivary glands/mucosa
    - Involvement of any other target organ

Grading system for assessing prognosis at diagnosis (on 151pts)

- Skin involvement > 50% of body surface area
- Progressive type onset of chronic GVHD
- Platelet count < 100,000/ul

Johns Hopkins Grading system for assessing prognosis

Risk Factors

- >50% skin surface
- Platelet <100,000/ul
- Progressive onset

CIBMTR cGVHD risk score (3550 pts)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age at transplantation</td>
<td></td>
</tr>
<tr>
<td>&lt; 29 y</td>
<td>0</td>
</tr>
<tr>
<td>30-59 y</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60 y</td>
<td>2</td>
</tr>
<tr>
<td>Prior acute GVHD</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Time from transplantation to cGVHD</td>
<td></td>
</tr>
<tr>
<td>≥ 5 mo</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 5 mo</td>
<td>1</td>
</tr>
<tr>
<td>Serum bilirubin at cGVHD onset</td>
<td></td>
</tr>
<tr>
<td>≤ 2 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 2 mg/dL</td>
<td>2</td>
</tr>
</tbody>
</table>
### CIBMTR cGVHD risk score (3550 pts)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet count at cGVHD onset</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; $100 \times 10^9$/L</td>
<td>1</td>
</tr>
<tr>
<td>$\geq 100 \times 10^9$/L</td>
<td>0</td>
</tr>
<tr>
<td><strong>Type of donor</strong></td>
<td></td>
</tr>
<tr>
<td>HLA-identical sibling/well-matched or partially matched URD</td>
<td>0</td>
</tr>
<tr>
<td>Other related/mismatched URD</td>
<td>1</td>
</tr>
<tr>
<td><strong>Disease status at transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
</tr>
<tr>
<td>Advanced</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sex mismatch (donor/recipient)</strong></td>
<td></td>
</tr>
<tr>
<td>Male/male, male/female, female/female</td>
<td>0</td>
</tr>
<tr>
<td>Female/male</td>
<td>1</td>
</tr>
<tr>
<td><strong>GVHD prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>CSA + MTX + other</td>
<td>0</td>
</tr>
<tr>
<td>Tacrolimus + MTX + other or T-cell depletion</td>
<td>1</td>
</tr>
</tbody>
</table>
Overall survival by cGVHD risk score.

Non Relapse Mortality by cGVHD risk score.
Application of the CIBMTR risk score to patients with systemically treated NIH chronic GVHD between 2006 and 2010 at 2 individual centers.

A

<table>
<thead>
<tr>
<th>CIBMTR (n=3550)</th>
<th>FCHRC (n=268)</th>
<th>PMH (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group</td>
<td>N</td>
<td>Proportion</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>0.025</td>
</tr>
<tr>
<td>2</td>
<td>1712</td>
<td>0.482</td>
</tr>
<tr>
<td>3</td>
<td>627</td>
<td>0.177</td>
</tr>
<tr>
<td>4</td>
<td>984</td>
<td>0.277</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>0.025</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>0.014</td>
</tr>
</tbody>
</table>

B

%Overall Survival vs. Years from Chronic GVHD

C

Cumulative Incidence of NRM, % vs. Years from Initial Systemic Treatment

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>No Symptoms</td>
<td>&lt;18% BSA with disease signs but NO sclerotic features</td>
<td>19-50% BSA OR involvement with superficial sclerotic features “not hidebound” (able to pinch)</td>
<td>&gt;50% BSA OR deep sclerotic features “hidebound” (unable to pinch) OR impaired mobility, ulceration or severe pruritus</td>
</tr>
</tbody>
</table>
Body areas used in NIH Consensus Scoring

NIH Assessment uses
Rule of 9s

8 body areas

Modified from Carpenter P A Blood 2011;118:2679-2687
NIH Consensus for Scoring of cGVHD

<table>
<thead>
<tr>
<th>Organ scoring of chronic GvHD</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
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Other sites:  Mouth  
Eyes  
Gastrointestinal tract  
Liver  
Lungs  
Joints and fascia  
Female genital tract
Documenting range of motion.
### NIH Consensus for Scoring and Global Assessment of cGVHD

**Organ scoring of chronic GvHD** - Tick relevant box for each organ and give result where indicated

<table>
<thead>
<tr>
<th>Number of organs</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 site</td>
<td>Score 1</td>
<td>Score 2</td>
<td>Score 3</td>
</tr>
<tr>
<td>2 sites</td>
<td>Score 1</td>
<td>Score 2</td>
<td>Score 3</td>
</tr>
<tr>
<td>3 sites</td>
<td>Score 1</td>
<td>Score 1</td>
<td>Score 3</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>Score 1</td>
<td>Score 1</td>
<td>Score 2</td>
</tr>
</tbody>
</table>

**Skin**
- SCORE 0: No Symptoms
- SCORE 1: <18% BSA with disease signs but NO sclerotic features
- SCORE 2: 19-50% BSA OR involvement with superficial sclerotic features “not hidebound” (able to pinch)
- SCORE 3: >50% BSA OR deep sclerotic features “hidebound” (unable to pinch) OR impaired mobility, ulceration or severe pruritus
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- **Local treatment**
- **Systemic treatment**

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<td>Score 2</td>
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How I conduct a comprehensive chronic graft-versus-host disease assessment.

Reliable Method for Comprehensive Chronic GVHD Assessment

Four Part Process

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>EXAM</th>
<th>OVERALL ASSESSMENT</th>
<th>LABS/TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>10 min</td>
<td>3 min</td>
<td>10-15 min</td>
</tr>
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</table>

Cumulative Data Completion (%)
Initial therapy of cGVHD

- Local treatment
- Steroid + Calcineurin inhibitor (standard of care)
- Supportive care
Randomized Trial of 307 patients
CSA+Prednisone versus Prednisone Alone

Avascular necrosis 12% in CSA+P versus 23% in P alone

Complications of long term steroid treatment

1. Avascular necrosis
2. Diabetes
3. Hypertension
4. Infections
5. Weight gain
6. Changes in body shape
7. Cutaneous atrophy and striae
8. Cataract
9. Osteoporosis
10. Emotional lability
11. Interference with sleep
A Model for Initial Treatment of chronic GVHD
Reaching Alternate Day Prednisone and CSA

Step 1

- Prednisone 1mg/kg/day
- CSA 2x5mg/kg/day

Step 2

Taper prednisone by 25% per week

Step 3

Taper CSA by 25% per week

Step 4

Step 5

after Vogelsang Blood 2001 97:1196-1201
Definition of steroid refractory cGVHD

- **Progression** on Prednisone at 1mg/kg/day for 1 month
- **No change** on >0.5mg/kg/day Prednisone for 2 months
- **Inability to taper** Prednisone below 0.5mg/kg/day

Evaluation of mycophenolate mofetil for initial treatment for chronic GVHD
A double blind randomized trial

MMF should not be added to the initial systemic treatment regimen of cGVHD

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Response %</th>
<th>Organ specific %</th>
</tr>
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<tbody>
<tr>
<td>Mycofenolate mofetil</td>
<td>46-75</td>
<td>Skin 53, mouth 67, liver 54</td>
</tr>
<tr>
<td>Extracorporeal photopheresis</td>
<td>61</td>
<td>Scler. skin 67, mouth 77, lung 54</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>63-94</td>
<td>Skin 65, mouth 75, liver 33, GI 67</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>65-70</td>
<td>Skin 63, mouth 48, liver 25, lung 38</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>20-38</td>
<td>Skin 46, Joint 78</td>
</tr>
</tbody>
</table>

Further possibilities

1. Pulsed high dose steroids (10mg/kg/day for 4 days)
2. Total Lymphoid Irradiation (1 Gy)
3. Alemtuzumab
4. Pentostatin
5. Revlimid
6. Anti IL-2 receptor Ab
7. Anti TNF receptor Ab
8. TKI (PDGF, TGF-beta) imatinib, nilotinib, dasatinib
Local treatment

- Dexamethasone oral rinses for mouth sensitivity
- Artificial tear, CSA drops for dry eyes
- Topical steroids and tacrolimus for localized skin involvement, lubrication of the dry skin with emollients etc.
Supportive Care

- **Infections – prophylaxis**
  - Encapsulated bacteria
  - Pneumocystis pneumonia
  - CMV
  - Varicella Zoster
  - Antifungal

- **Osteoporosis**

- **Hypertension**

- **Hyperglycemia**

- **Hyperlipidaemia**

- **Renal insufficiency**
cGVHD Should Be Managed by Multidisciplinary Team

- Transplant physician
- Dermatologist
- Ophtalmologist
- Dentist
- Dietician
- Pathologist

Consultants in:
- Rehabilitation medicin
- Gastroenterology
- Pulmonary medicine
- Neurology
- Infectious diseases
- Gynecology
Conclusions

1. cGVHD is a common (30% to 70%) complication after allo-HSCT and is a leading cause of late morbidity and mortality

2. Standard treatment is Steroid + Calcineurin inhibitor

3. Prolonged steroid use is required with <50% discontinuing immunosuppression by 2 years

4. There is no standard salvage therapy for cGVHD
Conclusions

6. cGVHD and its treatment are associated with sever complications including infections, osteoporosis, hypertension, hyperglycemia, hyperlipidemia and renal insufficiency.

7. Infections are the leading cause of death hence antimicrobial prophylaxis is necessary.

Los Balbases: The Miracle of Saints Cosma and Damian