ACUTE GHVD IN LIVER TRANSPLANT

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Case Presentation

- 60 yo man with HCV/HCC develops rash, mouth sores, abdominal pain three weeks after OLT
- Donor: Blood Type O, CMV - , EBV +
- Recipient: Blood Type O+, CMV +, EBV +
- HLA Mismatched at HLA I and II
- Standard immunosuppression with basiliximab (anti-CD25, IL2R), steroids, tacrolimus
- Routine infection prophylaxis
Case Presentation

- WBC 7 with normal differential, HCT 34, PLT 640
- AST 15, ALT 18, Alk Phos 386, T bili 1.5, INR 1.2
- Na 127, Cr 1.6
- Tacrolimus 5.1
- CMV -, HHV6 20,000
- Chimerism
  - CD3+ 25% donor
  - CD33+ 0% donor
Case Presentation

**FINAL DIAGNOSIS:**
A) Skin, right mid back, punch biopsy: Vacuolar interface dermatitis and mild telangiectasia, see comment.

**COMMENT:**
These histologic findings are consistent with grade II acute graft versus host disease. However similar histologic findings can be seen in erythema multiforme, lichenoid drug reaction, and viral exanthem. Clinical correlation is necessary.

**FINAL DIAGNOSIS:**
A) Duodenum, biopsy: Occasional apoptotic epithelial cells suggestive of graft-vs.-host disease of mild histologic activity (see COMMENT).

B & C) Antrum, biopsies: Rare apoptotic epithelial cells suggestive of graft-vs.-host disease of minimal histologic activity (see COMMENT).

D & E) Sigmoid, descending colon and rectum, biopsies:
1. Extremely rare individual apoptotic epithelial cells, suggestive of graft-vs.-host disease of minimal histologic activity (see COMMENT);
2. Pigmented histiocytes suggestive of melanosis coli.
Acute GVHD in OLT

- Rare complication of OLT with estimates from 0.1-2%
  - However, may be under-recognized/under-reported
- Can occur in other solid organ transplants, but most common in liver and small bowel transplants
  - $10^9$-$10^{10}$ leukocytes are present in the donor liver
- Largely fatal, with <80% of patients dying
  - Infection is most common cause of death

Symptoms of GVHD in OLT

- Typically occur 2-8 weeks after transplant
- Rash is often the presenting complaint
  - Present in >90% of cases
- GI complaints such as diarrhea, abdominal pain, ulcers
  - ~50%
- Liver is not involved
- Pancytopenia due to bone marrow infiltration/destruction of host stem cells
  - ~50%
Pathophysiology

- Large number of CD8+ T cells and NK cells are transplanted with the liver
- Host immunosuppression allows donor leukocytes to proliferate
- Donor lymphocytes typically persist for several weeks after transplant
  - *Low level chimerism is associated with increased graft survival*
  - *Trials of peri-operative donor BM infusions have shown decreased risk of rejection*
- In patients with GVHD, donor CD3+ is >10-20%
  - *High % of CD8+ donor cells*

Pathophysiology

- Pluripotent progenitors are also transplanted with the liver and can have hematopoietic potential
- *Liver is a site of fetal and extramedullary hematopoiesis*
- 65yo woman with cryptogenic cirrhosis gets liver transplant from 17yo male
  - Developed rash and pancytopenia 4 weeks later
  - Bone marrow was hypocellular (5%), peripheral blood HLA typing was donor-only
  - Counts improved with steroid, ATG but eventually died from multiple infections

Collins et al. NEJM 1993.
Pathophysiology

- Bone marrow had high % of male cells in multiple lineages

<table>
<thead>
<tr>
<th></th>
<th>Day 60</th>
<th>Day 101</th>
<th>Day 129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocyte/Macrophage</td>
<td>90%</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
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<tr>
<td>Lymphocyte</td>
<td>65%</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
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<tr>
<td>Granulocyte</td>
<td>66%</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
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<tr>
<td>Nucleated RBC</td>
<td>56%</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
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<tr>
<td>Megakaryocyte</td>
<td>0%</td>
<td>100%</td>
<td>100%</td>
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Collins et al. NEJM 1993.
Pathophysiology

Collins et al. NEJM 1993.
Pathophysiology—Risk Factors

- One-way HLA match with HLA-homozygous donor has ~50% risk of GVHD

Pathophysiology—Risk Factors

Recipient tissue

Donor lymphocyte

Recipient blood cell

Pathophysiology—Risk Factors

Recipient tissue

Donor lymphocyte

Recipient blood cell

Risk Factors
Treatment
# Treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
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<tr>
<td>Calcineurin inhibitors</td>
<td>Cyclosporine, Tacrolimus</td>
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<tr>
<td>Antimetabolites</td>
<td>Azathioprine</td>
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<tr>
<td>Alkylating agent</td>
<td>Cyclophosphamide</td>
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<td>Anti-T cell antibodies</td>
<td>ATG, OKT3, Alemtuzumab, Alefacept</td>
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<tr>
<td>Anti-B cell antibodies</td>
<td>Rituximab</td>
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<tr>
<td>Cytokine Inhibitors</td>
<td>TNF - Infliximab, Etanercept, IL2R – Daclizumab, Basiliximab</td>
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<tr>
<td>Immunoglobulin</td>
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<tr>
<td>Immune enhancers</td>
<td>Thymosin alpha 1</td>
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<tr>
<td>Cellular Therapy</td>
<td>Ex vivo T cell expansion, HSCT</td>
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Back to our patient...

- Started on high-dose methylprednisolone and given a dose of vedolizumab (anti-integrin $\alpha_4\beta_7$)
- Rapid resolution of rash and GI symptoms
- Chimerism studies one week after treatment showed 0% donor CD3+ cells
- Began rapid taper of steroids, did not receive a planned 2nd dose of vedolizumab
- No recurrent symptoms or lab abnormalities on follow up