Castleman Disease: The Role of Viral Infections

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CD and HIV

- HIV-infected patients frequently experience enlarged lymph nodes, which may be due to a wide variety of diseases
  - Many patients never have etiology definitively established
- In some cases, enlarged lymph nodes are due to CD
  - HIV patients with CD almost always have the M-PCV variant
- No relationship between CD4 count and onset of symptoms
- Role of HIV therapy unclear
  - Early reports of severe flares of MCD with the initiation of HIV therapy were not corroborated by subsequent studies
- Extremely increased risk of progression to aggressive non-Hodgkin’s lymphoma
  - 25% risk over 2 years found in the largest series
The symptoms seen in the first patients described to have CD led many to suspect viral etiology.

The human gamma-herpesviruses, Epstein-Barr Virus (EBV) and Human Herpesvirus 8 are both viral oncogens (viruses which can cause cancer), making them prime candidates for a role in the development of CD.
The Herpesvirus Family

- **HHV-1**: HSV-1
  - Clinical: Oral Herpes

- **HHV-2**: HSV-2
  - Clinical: Genital Herpes

- **HHV-3**: VZV
  - Clinical: Chickenpox

- **HHV-4**: EBV
  - Clinical: Mono, lymphoma

- **HHV-5**: CMV
  - Clinical: Retinitis

- **HHV-6/7**: Roseolovirus
  - Clinical: Exanthem subitum

- **HHV-8**: KSHV
EBV and CD

- Some of the cells observed in biopsy tissue from lymph nodes of patients with CD look similar to cells infected with EBV.
- Efforts to associate EBV with CD are challenging:
  - >90% of US population has been infected with EBV.
  - EBV often can reside in lymph nodes of healthy people for their entire life, so detecting EBV in lymph nodes of patients with MCD is not proof of causality.
- Currently, it is thought that there is no role for EBV infection in CD.
HHV-8 and CD

- Early series of patients with CD recognized an increased prevalence of Kaposi Sarcoma (KS)
- In 1994, human herpesvirus 8 was found to be the infectious agent responsible for KS
  - Member of the gamma-herpesvirus family, whose only other member infecting humans is EBV
HHV-8 Clinical Syndromes

- Kaposi’s Sarcoma
- Body Cavity Based Lymphoma
- Multicentric Castleman’s Disease
- Idiopathic Pulmonary Hypertension?
- Prostate Cancer?
- Multiple myeloma
- Sarcoid
HHV-8: Epidemiology

- Prevalence in the population varies by geography and demographic group
  - Men who have sex with men in the US and Europe: 25-30% of immunocompetent men and 55-75% of men infected with HIV
  - Geography: Seroprevalence among healthy adults in Southern Europe, Africa, the Middle East between 30-100%

- Unclear how virus is transmitted
  - Frequently found in saliva
  - Epidemiologic studies find that infection is correlated with sexual behavior in the US but the infection is usually acquired in childhood in Africa and the Middle East
Are All CD Patients Infected with HHV-8?

- No comprehensive study to document proportion of CD patients infected with HHV-8
  - Small studies suggest between 30-100%?

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV Status</th>
<th>CD Variant</th>
<th>Proportion HHV-8 Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soulier, et. al. (1995)</td>
<td>Negative</td>
<td>M-HVV</td>
<td>2/3 (66%)</td>
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<tr>
<td></td>
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<td>M-PCV</td>
<td>3/9 (33%)</td>
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<td>M-Mixed</td>
<td>2/5 (40%)</td>
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<tr>
<td></td>
<td></td>
<td>TOTAL</td>
<td>7/17 (41%)</td>
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<tr>
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<td>Positive</td>
<td>M-HVV</td>
<td>1/1 (100%)</td>
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<td>M-PCV</td>
<td>6/6 (100%)</td>
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<tr>
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<td>TOTAL</td>
<td>14/14 (100%)</td>
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<tr>
<td>Kikuta, et. al. (1997)</td>
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<td>Suda, et. al. (2001)</td>
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<tr>
<td>Yamasaki, et. al. (2003)</td>
<td>Negative</td>
<td>M-PCV</td>
<td>13/16 (81%)</td>
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</table>

HHV-8 and CD: Evidence for Causality

- In most other diseases associated with HHV-8, the virus can rarely be found in blood
  - In KS, HHV-8 is found in skin tumor or in saliva, but not in blood
- CD flares, however, are accompanied by dramatic rises in plasma HHV-8 levels, which decline with resolution of symptoms
- Treatment of CD with antiviral medications may result in resolution of symptoms
HHV-8 and IL-6

- HHV-8 encodes a gene which is a viral interleukin 6 (vIL-6) analogue which is transcribed actively during lytic infection
  - 50% similarity to hIL-6 on amino acid level
- vIL-6 complexes to the IL-6 binding protein, IL-6Rα, and binds the hIL-6 receptor, gp130
  
- Expression of vIL-6 also stimulates hIL-6
HHV-8 and IL-6 (continued)

IL-6 leads to stimulation enumeration and stimulation of plasma cells to cause increased immunoglobulins, plasmacytomases or enlarged lymph nodes.

VEGF leads to angiogenesis and endothelial cell proliferation.
Unified Model of CD Pathogenesis

- HHV-8 Infection
- IL-6 Gene Promoter Polymorphisms
- Alteration of IL-6 Cell Signaling Pathway

Increased IL-6 Production

- Lymphocyte Proliferation
- Organomegaly
- Capillary Leak

Antivirals

- Monoclonal Anti-IL-6 Antibody

Lymphoma

- Ig Dysregulation

Rituximab & / or Chemotherapy

- Sepsis
- POEMS

- Pulmonary Edema
- Renal Insufficiency
Antiviral Therapy and HHV8

**In vitro studies**
- Many antitherpetic antivirals have efficacy against HHV-8 in a test tube
  - Cidofovir > ganciclovir > foscarnet > famciclovir > aciclovir

**Observational Studies**
- AIDS patients with CMV retinitis receiving ganciclovir had a 40% reduction in odds of developing KS

**Clinical Studies**
- Cidofovir was ineffective in treating HIV-associated KS
- Both valganciclovir and ganciclovir was effective in reducing HHV-8 viremia and inducing a complete remission of Multicentric Castleman Disease
To date, 12 patients have been treated through 21 “flares” of MCD with valganciclovir

<table>
<thead>
<tr>
<th>#</th>
<th>Gender</th>
<th>Age</th>
<th>Flares to Date</th>
<th>HIV Status</th>
<th>CD4 Count (If HIV-Positive)</th>
<th>HIV RNA (If HIV-Positive)</th>
<th>HHV-8 Antibody Status</th>
<th>HHV-8 Viremia During Flare?</th>
<th>Treatment with GCV</th>
<th>Clinical Response</th>
<th>Virologic Response</th>
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</table>

Age, HIV Infection Status, HIV RNA, HHV-8 Antibody, Ganciclovir Treatment and Responses Apply to First Flare
Reduction in HHV-8 Viral Load with Ganciclovir in Multicentric Castleman Disease

Brown line indicates either treatment with valganciclovir (Patients 2-5) or intravenous ganciclovir (Patient 1)

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