The Clinical Spectrum of Herpesvirus Infections

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Objectives

- Recognize the herpesviruses that cause disease in humans
- Understand the clinical presentations of herpesvirus infections
Herpesviruses overview

- > 100 known herpesvirus
  - 8 human herpesviruses
- Greek word herpein – "to creep or crawl"
  - referring to the latent, recurring nature
- All herpesviruses can establish latent infection within specific tissues, characteristic for each virus

History of herpesviruses

- 400 BC – Herpes infection described by Hippocrates
- 1875 – Varicella determined to be infectious
- 1800 – Varicella isolated in culture
- 1900 – 1954 – link between Burkitt’s lymphoma and infection first suggested
- 1956 – CMV discovered
- 1964 – EBV identified in patients with Burkitt’s
- 1986 – HHV-6 discovered in patients with lymphoproliferative disorders
- 1990 – HHV-8 identified in biopsies from Kaposi’s sarcoma
- 1994 – HHV-7 identified in healthy individual
Herpesviridae Subfamilies

**Alphaherpesvirinae**  
*(HSV-1, HSV-2, VZV)*  
- Broad host range  
- Rapid reproductive cycle,  
- Cytopathic effect and spread in culture  
- Latent infections: Neuronal (sensory ganglia)

**Betaherpesvirinae**  
*(HCMV, HHV-6,7)*  
- Restricted host range  
- Slow reproductive cycle  
- Latent virus: Leukocytes (CD34+), Hematopoetic stem cells, and secretory glands (Salivary glands, and renal tubule).

**Gammaherpesvirinae**  
*(EBV, KHSV)*  
- Most Restricted Host Range  
- Replicate in lymphoblastoid Cells  
- Viruses specific for B or T cells  
- Latent or lytic infection
Shared properties of human herpesviruses

- Code for unique enzymes involved in the biosynthesis of viral nucleic acids
- Synthesis and assembly of viral DNA is initiated in the nucleus
- Release of progeny virus from the is accompanied by cell death
- Establish latent infection within tissues

HHVs can cause severe and atypical disease in immunocompromised patients

**Immunosuppression**
- Medications
- HIV
- Cancer/ Transplant

**Host Barrier defects** (MUCOSITIS, Eczema, Burns)

**Immune defects**
- Neonates
- Pregnancy
- Elderly
- Cellular defects
Diagnosis of Herpesviruses

• Isolation virus through culture and/or detection of viral genes or gene products
• Direct visualization
• Serology
• Polymerase chain reaction

Case #1

• A 4 year old F presents to your office with a swollen, painful, right index finger. You notice multiple fluid-filled lesions on the finger, as well as some small ulcers on her tongue and bleeding around her gums. What’s the diagnosis?

Image courtesy of Dwight Powell
HSV - Pathogenesis

Primary infection: high titer and prolonged infection

Establish Latency: provide reservoir and viral template for future secondary infections

Secondary Reactivation: lower titer and shorter duration but there are some who have more prolonged disease

Clinical Manifestations of HSV

Modified from image CC BY 3.0
Tonye A. Ogle OpenStax CNX
Download for free at: http://cnx.org/content/1a4a3bd1-f368-4827-985e-7f6e1babdef@1
Diseases Caused by HSV: Oral & Cutaneous

Images courtesy of Dwight Powell

HSV Gingivostomatitis in Immunocompromised
Images courtesy of Dwight Powell

Percent of U.S. population positive for herpes viruses: 2005-2010

Bradley et al, JID 2013
Case #2

- An unimmunized, previously healthy 25-year-old woman presents to your office with a 24-hour history of fever, malaise, and a generalized pruritic rash. Physical examination reveals a temperature of 38.6°C, respiratory rate of 25 breaths/min, heart rate of 88 beats/min, and blood pressure of 110/62 mm Hg. She has a papulovesicular rash over her face, trunk, and extremities that involves her scalp but spares her palms and soles. The remainder of her exam is normal. What is your diagnosis?
Case #2: Papulovesicular Facial Rash*

*Courtesy of Red Book Online.® 2009

Case #2: Papulovesicular Truncal Rash*

*Courtesy of Red Book Online.® 2009
**Varicella-Zoster Virus (VZV)**

**Pathogenesis Primary infection**

- **Entry:** Respiratory route
  - Local replication
- **Primary viremia:** seeds liver/spleen
  - T cells and Antibodies limit primary viremia in people with prior immunity
- **Secondary replication cycle**
  - Amplification Liver and Spleen
- **Secondary viremia** hematogenous dissemination to cutaneous sites.
- **Immunity:** T-cell response and resolution of lesions, IgG present
- Virus establishes latent virus in dorsal root ganglia

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**Varicella-Zoster Virus**

- **Transmission:** direct contact or aerosol
- **Incubation**
  - Mean 14-16 days (10-21 days)
  - Contagious 1-2 days before rash and until lesions crusted
- **Increased severity**
  - Immune compromised
  - Older age
  - Pregnancy
- **250-500 lesions wild-type infection; in immunized, ≤ 50 lesions**
Herpes Zoster

GABHS periorbital cellulitis and necrotizing fasciitis complicating varicella
Necrotizing Fasciitis

Case #3

• A 1 day old male is born to a mother with no significant prenatal history. Delivery is uncomplicated but initial examination reveals hepatosplenomegaly and a “blueberry muffin” rash. Labs show thrombocytopenia and elevated liver enzymes. What’s your diagnosis?
Cytomegalovirus Clinical Syndromes

- Congenital infection
- Mononucleosis syndrome
- Immunocompromised hosts: may develop life-threatening disseminated disease

CMV Seroprevalence

Congenital CMV

- Hepatosplenomegaly
- Retinitis
- Rash
- Central nervous system involvement

- Leading nongenetic cause of sensorineural hearing loss in US
  - Up to 50% of symptomatic infants
  - Up to 15% of asymptomatic infants

CMV Clinical Manifestations

- 90% asymptomatic
- Mononucleosis syndrome (20-50% cases)
  - Fever - most prominent
  - Increased SGOT/SGPT (90%)
  - Rash, particularly following ampicillin (EBV>CMV)
  - Atypical lymphocytosis
  - Exudative pharyngitis (EBV >> CMV)
  - Hepatosplenomegaly (EBV > CMV)
  - Adenopathy (EBV > CMV)
  - Aseptic meningitis, encephalitis, G B Syndrome
CMV – Immunocompromised Hosts

- Arthralgia
- Leukopenia
- Pneumonitis
- Retinitis
- Enterocolitis
- Polyradiculopathy
- Deterioration of graft function

Case #4

- A 15yo male presents to your office with fever, sore throat, and swollen glands in the neck. Exam reveals exudative pharyngitis, bilateral cervical adenopathy, and mile hepatosplenomegaly. What’s your diagnosis?
Epstein-Barr Virus

- Present in human populations from all parts of the world
- Acquisition occurs at an earlier age in underdeveloped countries
  - Adolescent seroprevalence:
    - Undeveloped: >90%
    - Developed: 40-50%

EBV

Clinical Manifestations - Acute
- Asymptomatic (frequency inversely related to age)
- Mononucleosis syndrome
- Neurologic/Neuropsychiatric
  - Nerve palsy, esp. Bell’s palsy
  - Guillain-Barré Syndrome
  - Aseptic meningoencephalitis
  - Transverse myelitis
  - “Alice-in-Wonderland” Syndrome
- Thrombocytopenia/purpura
EBV Mononucleosis Syndrome

- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis
- Skin rash

- Pneumonitis
- Neurologic
- Myocarditis/pericarditis
- Thrombocytopenia
- Anemia
- Granulocytopenia
# EBV Complications

- Splenic rupture
- Airway obstruction
- Fulminant hepatitis
- Myopericarditis
- Meningoencephalitis
- Thrombocytopenia
- Hemolytic anemia
- Orchitis

# EBV in Immunocompromised Hosts

- X-linked lymphoproliferative syndrome
- Post-transplant B cell lymphoproliferative disorders
- HIV-associated B cell lymphoma
- HIV-associated oral “hairy” leukoplakia
- HIV-associated LIP
- HIV-associated leiomyosarcoma
EBV-associated malignancies

- Burkitt lymphoma
- Nasopharyngeal carcinoma
- Hodgkin’s disease (some are EBV-associated)
- HIV-associated
  - B cell, non-Hodgkin lymphoma
  - Smooth muscle (leiomyoma, and leiomyosarcoma)
- Lymphoma

EBV Seroprevalence

![Graph showing EBV seroprevalence by age and ethnicity]

EBV Seroprevalence

Diagnosis of EBV

- Direct visualization
- Serology
- Polymerase chain reaction

*Courtesy of Red Book Online.® 2009
Case #5

- A 13-month-old female developed high fever that persisted for 4 days without recognized cause. The child appeared relatively well and the fever subsided to be followed by a maculopapular rash that began on the trunk and spread to involve the face and extremities. What’s your diagnosis?

Human Herpesvirus 6 & 7

- Human herpes viruses 6 and 7 are associated with exanthem subitem (roseola) and rejection of transplanted kidneys

- Antibodies to this HHV-6 present in almost everyone by age 5

- HHV-7 ubiquitous: >95% of adults seropositive

- HHV-6 can also be recovered in vivo from a broad range of tissues
HHV-6 Clinical Manifestations

- High fever
- Irritability
- Adenopathy (cervical and occipital)
- Maculopapular rash
- Inflamed tympanic membranes
- URI symptoms
- GI symptoms: vomiting and diarrhea
- Bulging anterior fontanelle
- Febrile seizures (15%)

HHV-6 Less Common Manifestations

- Arthritis
- Hepatitis
- Heterophile - negative mononucleosis (primarily adults)
- Intussusception
- Thrombocytopenia
- Neurologic (aseptic meningitis, meningoencephalitis, multiple sclerosis)
- Syndromes in immunocompromised patients
  - Suppression of marrow in BMT
  - Interstitial pneumonitis in BMT/HIV
  - Organ dysfunction/graft rejection
  - Skin rash
HHV-7 Clinical Manifestations

- Fever
- Maculopapular rash
- Irritability
- Lymphadenopathy
- Mild diarrhea
- Hepatitis

Case #6

- A 34 year old HIV+ male presents to your office with complaints of a lump in his mouth. He has been noncompliant with medications, his viral load is >2 million copies/ml and his CD4 lymphocyte count is 143 cells/mm³. Exam reveals a firm, fleshy lump on the hard palate.

- What’s your presumptive diagnosis?
Human Herpesvirus 8

- Kaposi’s sarcoma-associated herpesvirus (KSHV)
- Manifestations of 1° infection not well characterized
- HHV-8 is implicated as the etiologic agent of:
  - Kaposi’s sarcoma (HIV+/HIV-) (found in 95%)
  - Monoclonal B cell lymphomas in HIV
  - Multicentric Castleman’s disease

HHV-8 Epidemiology

<table>
<thead>
<tr>
<th>Population</th>
<th>Seropositivity Rate</th>
</tr>
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<tbody>
<tr>
<td>US Children</td>
<td>2 - 8%</td>
</tr>
<tr>
<td>US adults</td>
<td>25%</td>
</tr>
<tr>
<td>US HIV+ IVDU</td>
<td>23%</td>
</tr>
<tr>
<td>US HIV+ women</td>
<td>21%</td>
</tr>
<tr>
<td>US HIV+ homosexual men</td>
<td>90%</td>
</tr>
<tr>
<td>US HIV+/KS+</td>
<td>96%</td>
</tr>
<tr>
<td>African endemic KS</td>
<td>100%</td>
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The take-home message...

Love May Not Last But Herpes Is Forever