CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Human Herpesviruses Family
1. Herpes simplex virus type 1 (HSV-1)
2. Herpes simplex virus type 2 (HSV-2)
3. Varicella-zoster virus (VZV)
4. Epstein-Barr virus (EBV)
5. Cytomegalovirus (CMV)
6. Human herpesvirus type 6 (HHV-6)
7. Human herpesvirus type 7 (HHV-7)
8. Human herpesvirus type 8 (HHV-8)

“Mononucleosis Syndrome”
- Clinical Features:
  - Fever
  - Malaise
  - Myalgias, arthralgias
  - Pharyngitis
  - Lymphadenopathy
  - Hepatomegaly / splenomegaly
- Laboratory Findings:
  - Lymphocytosis (>50%; >4500/mm3)
  - Atypical lymphocytes (>10%)
  - Abnormal LFTs

Differential Features of Most Common Causes of Mononucleosis Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>EBV</th>
<th>CMV</th>
<th>Toxo</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Fever</td>
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<tr>
<td>Myalgias / Arthralgias</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>Sore throat</td>
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<td>Exudative pharyngitis</td>
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<td>Headache</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Splenomegaly</td>
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<td>Hepatomegaly</td>
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<td>Atypical lymphocytes</td>
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<td>Elevated LFTs</td>
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</table>
Non-ID causes of mononucleosis syndrome with atypical lymphocytosis

- Drug hypersensitivity syndrome
- Can be induced by several drugs:
  - anticonvulsants such as phenytoin, carbamazepine
  - antibiotics such as isoniazid, minocycline

Epstein Barr Virus: Epidemiology

- Majority of infections are asymptomatic in early childhood
- Adolescent seroprevalence:
  - Resource limited regions >95%
  - Higher resource regions ~40-50%
- Primary infection in adolescents or adults results in ~50% symptomatic dz (infectious mononucleosis)
- 500 cases/100,000 population/year in USA
  - incidence rate for those 15–19yo estimated 200 – 800 cases per 100,000
- Occasionally transmitted by transfusion or organ/stem cell transplant

EBV Infection: Pathogenesis

- Gamma herpesvirus; HHV-4
- Infectious virus intermittently shed from oropharyngeal epithelial cells
  - Up to 6 months or longer after disease, then intermittently
- Transmission by saliva (“kissing disease”), sexual transmission possible
- Long incubation period – 4 to 8 weeks
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy
  - EBV reactivation mostly asymptomatic

Infectious Mononucleosis

- Etiology - primary Epstein-Barr virus infection
- Transmission - saliva (due to prolonged shedding for months)
- Clinical – viral prodrome with fever, malaise, headache
  - Pharyngitis with tonsillar exudate
  - Symmetrical cervical adenopathy, posterior > anterior
  - Palatal petechiae, periorbital edema, and rash (maculopapular, urticarial, or petechial)
  - Splenomegaly in 15 to 65% of cases
- Acute symptoms persist 1-2 weeks, fatigue can last for months
- Lab - lymphocytosis with atypical lymphocytes
  - Diagnosis - serologic. Non-specific heterophile Ab (“monospot”); specific Ab (VCA, EBNA)
  - Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine

Complications of Primary EBV Infection/Infectious Mononucleosis

- Splenic rupture in 0.5-1%, male > female, mostly w/in 3 weeks (up to 7)
  - Avoid contact sports for 4 weeks minimum
- Prolonged fatigue/malaise (>6 mo. in 10%)
- Airway obstruction from massive adenopathy
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess

Heme syndromes:
- Neutropenia
- TTP-HUS
- DIC
- Acquired hypogammaglobulinemia
- X-linked lymphoproliferative disease (EBV as trigger)
- Hemophagocytic lymphohistiocytosis (HLH) (est 50% of all HLH cases from EBV)
• Viral meningitis
• Encephalitis
• Optic neuritis
• Transverse myelitis
• Facial nerve palsy

• Gullain–Barre syndrome
• Acute cerebellar ataxia
• Hemiplegia
• Sweaty palms
• Psychoses

• PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

• WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis

• If EBV viremia, reduce immune suppression whenever possible

• High risk for EBV syndromes and proceeding to post-transplant (1 to 5% of cases)

• No evidence that any current antiviral therapy is helpful

• Elevated liver function tests
  • AST, ALT (80%), alkaline phosphatase (60%)
  • Elevated bilirubin less common (45%, but jaundice in <10%)

• EBV viral load/PCR - not necessary for routine mononucleosis, may be useful in transplant or other immunocompromised patients

• Elevated white blood cell count averages 12,000 to 18,000/microL

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Spontaneous EBV reactivation requiring evaluation

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Epidemiology of CMV Infection
- Age-specific peaks in incidence:
  - Children in USA: 10-15% infected before age 5
  - Young adults at onset of sexual activity
  - ~50% adults are CMV IgG+ (NHANES, Bate et al. Clin Infect Dis 2010)
- Seroprevalence of CMV correlates inversely with socioeconomic development
- In the developing world, CMV seroprevalence approaches 100%.
- Transplant:
  - Organ: highest risk is donor seropositive, recipient seronegative (D+R-)
  - Stem cell: highest risk is D-R+ (opposite)
  - Superinfection can occur (organ transplant D+R+ higher risk than D-R+)

Transmission & Pathogenesis of CMV
- Beta herpesvirus
- Infection transmitted via:
  - Body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - Transplanted tissue (blood, organs, stem cell transplant)
  - Reduced with routine use of blood filtered/WBC-depleted
- Primary infection usually asymptomatic/subclinical
- Mononucleosis syndrome in <10%
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses.
  - Ongoing shed is important factor in transmission
- No vaccine available; several under development

CMV Mononucleosis Syndrome
- CMV causes ~20% of mono syndrome cases in adults
- Presentation: fever, myalgias, atypical lymphocytosis.
  - High fever ("typhoidal"). Pharyngitis and lymphadenopathy (13-17%) less common than with EBV (80%).
  - Rash in up to 30% (variety of appearances)
  - May be clinically indistinguishable from mono syndrome caused by other pathogens
  - Complications: colitis, hepatitis, encephalitis, GBS, anterior uveitis
  - Symptoms may persist > 8 weeks
  - Diagnosis: IgM/IgG seroconversion (CMV blood PCR - can be confusing)
  - Antiviral therapy not indicated (except for severe complications or in immunocompromised)
CMV: Congenital infection

- Leading cause of nonhereditary sensorineural hearing loss
- Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in developed countries
- 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk
- Infants more likely to have symptoms at birth & long-term sequelae
- Reactivation maternal CMV infection - 0.9-1.5% risk
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

CMV INFECTION AFTER ORGAN TRANSPLANT: A SPECTRUM OF DISEASE

Asymptomatic
- CMV Viral Syndrome
  - Flu-like syndrome: fever, malaise, myalgia
  - Leukopenia, thrombocytopenia
- Flu-like illness

Tissue-Invasive Disease
- GI diseases: Colitis, Hepatitis, Pneumonitis, Myocarditis, Myocardiitis, Nephritis, Encephalitis, retinitis

CMV Guidelines, Transplantation 2018

PROPHYLAXIS: Prophylaxis vs. Preemptive Therapy

- Antiviral prophylaxis
  - Prophylaxis period (typically 3–6 months) after transplantation
  - Weekly plasma CMV DNA testing is recommended in life-threatening & severe transplant rejection

- Preemptive monitoring period (once weekly for 12–16 weeks)
  - If CMV is detected (PCR or pp65 Ag), treat until CMV is cleared

CMV Diagnostics

- Serology
  - To diagnose acute infection, detect IgM or IgG → IgM seroconversion
  - CMV IgG establishes donor/recipient serostatus/risk in transplantation (no IgM)

- Molecular diagnostics
  - Quantitative PCR – detects CMV DNA in blood, other fluids, tissues
  - Lower (somewhat) sensitivity of blood PCR for CMV GI disease, pneumonitis, retinitis

- Histopathology of biopsied tissue
  - Basophilic intranuclear inclusion bodies surrounded by a clear halo – “owl’s eye” CMV inclusions
  - CMV-specific immunohistochemical stains

TREATMENT for Transplant Recipients: Consensus Recommendations (Kotton et al, CMV Guidelines, Transplantation 2018)

- For Ongoing CMV disease, either oral valganciclovir (450 mg every 12 hours) or intravenous GCV (5 mg/kg every 12 hours) are recommended as first-line treatment in adults with normal kidney function
- Valganciclovir is recommended in patients with mild to moderate CMV disease
- Intravenous GCV is recommended in life-threatening & severe CMV disease; after clinical response, intravenous GCV may be transitioned to VGCV
- In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral loads, and cytopenia

Risk Factors

- Inadequate antiviral drug dose or delivery
- Prolonged antiviral drug exposure
- Ongoing active viral replication (often seen w/ lack of prior CMV immunity D+/R-)
- Strongly immunosuppressive therapy
- Drugs with lower barrier to resistance

Rates

- Among solid organ recipients the usual incidence of resistance after ganciclovir therapy is 5% to 12%, but up to 18% in lung and 31% in intestinal and multivisceral organ transplant recipients
- Incidence of resistance is lower, in the 0 to 3% range, with 100 to 200 days of ganciclovir or valganciclovir prophylaxis in D+/R- kidney recipients (IMPACT trial, Humar AIT)
Resistant CMV Management: Guidelines


Human Herpesvirus Type 6

- Beta herpesvirus, discovered in 1986
- Two subgroups:
  - HHV-6A – uncommon pathogen, little known about clinical impact or epidemiology
  - HHV-6B – frequent infection in healthy children, etiology of roseola (exanthem subitum), & cause of reactivation disease
- Primary infection common in first year of life, >60% infected by 12 months
- Transmission by saliva; incubation period ~9 days (5-15 days)
- Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- Can integrate into human germline cells (1%); chromosomally inherited, will be viral load/PCR high level positive forever; can reactivate from integrated state
- No vaccine available or under development

Exanthem subitum (roseola, sixth disease)

Slide courtesy of John W. Gnann Jr., MD, Medical University of South Carolina

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31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients

Speaker: Camille Kotton, MD

Human Herpesvirus Type 6: Normal Hosts
- Associated syndromes
  - Exanthem subitum (roseola infantum, sixth disease)
  - Children <4 yo; high fever for 5 days (febrile seizures), followed by a rash
  - Primary infection in adults (very rare) – mononucleosis syndrome
  - Reactivation disease in transplant patients, esp. encephalitis and pneumonitis
  - Mesial temporal lobe epilepsy association
  - Not the cause of MS, chronic fatigue, myocarditis, some others

- Diagnosis
  - Classic rash and clinical setting (early childhood)
  - IgG seroconversion
  - PCR from plasma (cell free), CSF, tissue → immunocompromised patients

- Therapy
  - Supportive care

HHV-6: Immunocompromised Hosts
- Associated syndromes
  - Reactivation disease in transplant patients
  - Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days
  - Bone marrow suppression (maybe also GVHD?)
  - Pneumonitis (rare, harder to prove)

- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
  - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
  - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-20,000 copies/ml
  - Encephalitis – MRI, EEG

- Therapy
  - Ganciclovir or foscarnet; likely decide based on toxicities; cidofovir last choice
  - Treat encephalitis; not all need treatment, not low level HHV-6+ in blood
  - Reduce immunosuppression if possible

Human Herpesvirus Type 8
- Gamma herpesvirus, discovered 1994
- Kaposi sarcoma-associated herpesvirus (KSHV)
- Four variants have been described:
  - Classic
  - Endemic (Africa, Mediterranean regions)
  - Iatrogenic or immunosuppression-associated
  - Epidemic/AIDS-associated

- HHV-8 seroprevalence in the US (highly variable internationally):
  - Blood donor populations: 1-5%
  - MSM: 8-25%
  - HIV-positive MSM: 30-77%
  - HIV-positive with KS: 90%

- Route of transmission unknown – Sexual, saliva?
  - Transmission via SOT documented (rare).

- 1° infection usually asymptomatic, some with febrile rash syndrome

HHV-8 Associated Diseases
- Kaposi sarcoma, 4 types:
  - Classic: indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - Endemic: all parts of equatorial Africa, affecting both children and adults, can be more aggressive than classic
  - Transplant-associated: more often donor-derived (D+R-), can be reactivation
  - Epidemic/AIDS-related: KS is the most common tumor arising in people living with HIV; an AIDS-defining illness

- Primary effusion lymphoma (body cavity-based lymphoma)
  - Non-Hodgkin B-cell lymphoma, usually in HIV+.
  - Involves pleural, pericardial, or peritoneal spaces

- Castleman’s disease (HHV+ and HIV-)
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related.
  - Fever, hepatomegaly, splenomegaly, massive lymphadenopathy

- KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+:
  - Fever, elevated IL-6 & IL-10, high HHV-8 VL. High mortality rate.

HHV-8 Diagnosis and Treatment
- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman’s disease, etc

- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi’s sarcoma treated as a cancer
**31 – CMV, EBV, HHV6 and HHV8 in Immunocompetent and Immunocompromised Patients**

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### Antiviral Prophylaxis & Treatment Agents

<table>
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<tr>
<th>Antiviral agent</th>
<th>EBV</th>
<th>CMV</th>
<th>HHV-4</th>
<th>HHV-6</th>
<th>HHV-8</th>
<th>HSV</th>
<th>Varicella</th>
<th>BK</th>
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<tr>
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* *acyclovir/valacyclovir/famciclovir and foscarnet for prophylaxis only
** foscarnet, cidofovir not usually used for prophylaxis

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### Summary: EBV, CMV, HHV-6, HHV-8

- **Common childhood infections**
- **All human herpesviruses establish latency**
- Serology useful, viral load detection more helpful in immunocompromised
- Infection from donor → recipient usually major risk factor
- Varied spectrum of clinical manifestations, from infectious syndromes to malignancies (EBV, HHV-8)
- Antiviral prophylaxis/treatment – best for CMV, more limited utility for others
- No vaccines available

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Questions? ckotton@mgh.harvard.edu

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