Epstein-Barr Virus in a Toddler

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Disclosure

- Presenter: Elaine Bullock, MD

- I have nothing to disclose regarding this topic.
Objectives

• For learners to be able to recognize the various presentations of Epstein-Barr Virus

• Evaluate the diagnostic studies available and the strengths and weaknesses of each
Case

A 22 month old female presented to her pediatrician for follow up a week after being seen in the emergency department for lymph node swelling and fever >101 F. She was treated with IM Rocephin and instructed to follow up with her PCP.

During her follow up visit, concern for worsening cervical lymphadenopathy and deficient vaccination status led to testing for mumps. The IgM returned positive on day 8 of illness, at which time she was admitted to the hospital for further management and work up.
Past Medical History

PMH: Tympanostomy tubes placed one month prior due to recurrent acute otitis media. Eczema.

Birth: term via c-section due to non-reassuring fetal heart tones. Uncomplicated newborn nursery stay


Social: Lives at home with mother, father, and one older half sibling. Live outside city limits. No pets. No known farm animal contacts or recent zoo visits. No recent swimming or travel. Does attend in-home day care with 3 other children. Dad hunts and occasionally takes children into woods with him but no known tick exposures.

Immunizations: Delayed. Had not yet received 6 or 12 month vaccinations
Hospital Course

At admission she was found to be anemic and leukopenic.

Immunoglobulins were sent and all (IgM, IgG, IgA, IgE) returned significantly elevated for age.

Pediatric Infectious Disease was consulted by phone
Differential

- Noninfectious
  - Autoimmune Disease
  - Oncologic Disease
  - Collagen and Vascular Disease

- Infectious
  - CMV
  - EBV
  - Adenovirus
  - Mycoplasma
  - Rickettsia
  - Viral Hepatitis
  - HIV
  - Rubella virus
  - Streptococcal pharyngitis
Pediatric ID team recommended obtaining Mycoplasma, EBV viral load due to elevation of immunoglobulins, and respiratory panel that returned + rhino/enterovirus. Patient was then started on Doxycycline for empiric Rickettsia coverage.

During admission, her respiratory status worsened and she was transferred to PICU where cervical, axillary, and inguinal lymphadenopathy was found to be worse with new hepatosplenomegaly.

CT chest, abdomen and pelvis was obtained and only positive for pulmonary infiltrates.
Hospital Course

On day 12 she went to OR for CVL placement. During induction of anesthesia she developed bronchospasm, hypotension and bradycardia. She required dopamine and was subsequently intubated.

Blood type and screen returned + cold autoglobulins and direct coombs was negative when cells were pre-warmed.

On day 14 she was transferred to University Health for higher level of care.
Hospital Course

EBV PCR values from admission returned elevated at 20,600 genome copies/ml and trended down to 9100 genome copies/ml over 2 week time period

Cold agglutinins titers trended down from 1:512 to 1:256.

Over course of hospitalization her ANC progressively declined to point of severe neutropenia, 399.

With decreasing titers and improved clinical condition she was discharged home on Amoxicillin to complete 10 day course for pneumonia with close hematology follow up.
26 days later the patient presented to ED with fever and neutropenia. Found to have pneumonia with increasing EBV viral load to 15,800 genome copies/ml in the blood.

Started on broad spectrum antibiotics, but after no improvement with antibiotics, bronchoscopy with VATs (video-assisted thoracoscopic surgery) was performed.

Pathology of pulmonary nodes returned with atypical B-cell lymphoproliferative disease with EBV; consistent with diffuse large B-cell lymphoma.

Was later transferred to St. Jude Children’s Hospital for chemotherapy
Epstein-Barr Virus
*Gamma herpesvirus*

- Humans are the only known reservoir

- Approximately 90% US citizens are seropositive by age 30.

- Acquired through saliva, transplants and blood transfusions. EBV replicates in oral epithelial cells, which eventually lyse and release virions that spread to target B cells in blood, lymphatic system, liver and spleen.

- The incubation period is 30-50 days.

- Can still be shed in saliva at high concentrations for 6 months following acute infection and at lower concentrations for life.

- After the primary infection EBV becomes latent in host.
Spectrum of Clinical Disease

- Asymptomatic
- Infectious Mononucleosis
  - Malaise and myalgia
  - Fever
  - Pharyngitis with petechiae or exudates
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Headache
  - Rash
- Fever of Unknown Origin
- Cancers
- Posttransplant lymphoproliferative disease (PTLD)

[http://www.dovemed.com](http://www.dovemed.com)
Diagnosis

- **Nonspecific Testing**
  - Heterophile antibody Testing (Monospot)
    - IgM antibodies directed against mammalian erythrocytes. Appears during the first two weeks of illness and declines slowly over 6 month period.
    - Children under the age of 4 do not have the ability to develop high enough titers to mount response; therefore it is not recommended for diagnosing younger children
    - Can identify 85% of classic infections in older children and adults during the second week of illness, but false positives do exist
  - Atypical Lymphocytes
    - Mature CD8+ T cells
    - Increases during second week of illness.
    - If >10% atypical lymphocytes in combination with + heterophile antibody test can be diagnostic
Viral Capsid Antigen

- VCA IgG Ab occurs in high titers early in infection and will persist for life.
- May not be helpful in determining acute infection.

Viral Capsid Antigen

- VCA IgM Ab appears early.
- Detected for 4-8 weeks, making it valuable in diagnosing acute infections.

(Red Book, 2015)
Epstein-Barr Nuclear Antigen (EBNA)
- Antibody is not present until several weeks to months after illness and persist for life
- Marker for past infection

Early Antigen (EA)
- Anti-EA appears early and disappears around 3-6 months
- Not as reliable and therefore is not included in some of the newer panels

(Red Book, 2015)
Complications of EBV

- Acute
  - Aseptic meningitis, encephalitis, myelitis, optic neuritis, CN palsies, transverse myelitis, Guillain-Barre Syndrome, Multiple Sclerosis
  - Tonsillar swelling
  - Subclinical hepatitis
  - Splenic rupture
  - Mild thrombocytopenia, agranulocytosis, hemolytic anemia with + Coombs and cold agglutinins
  - Pneumonia, orchitis, myocarditis are uncommon
Complications

- **Chronic**
  - Posttransplant lymphoproliferative disease (PTLD)
    - The immunosuppression required to prevent graft rejection post transplantation can potentially allow for uncontrolled proliferation of EBV-infected B-cells, which may result in a spectrum of B-cell proliferations that range from hyperplasia to true lymphoma.
  - X-linked lymphoproliferative Disease (XLP)
    - Disorder of the immune system with an exaggerated immune response to EBV
    - The exaggerated proliferation of immune cells can lead to a life-threatening reaction called hemophagocytic lymphohistiocytosis.
- **Malignancy**
  - Nasopharyngeal carcinoma, Burkitt’s Lymphoma, Hodgkin’s Lymphoma
Treatment

- Supportive care is mainstay of treatment for infectious mononucleosis
  - Avoid amoxicillin and ampicillin, 80-90% will result in morbilliform rash
  - No contact sports for the initial 2-3 weeks of infection or until splenomegaly resolves

- Antivirals (acyclovir) have no proven value

- Steroids may be indicated in certain circumstances
  - Airway obstruction due to tonsillar swelling
  - Severe thrombocytopenia with risk of bleeding
  - Seizures and Meningitis
  - Myocarditis
  - Hemolytic anemia, or HLH
EBV is a common childhood infection which rarely causes illness in toddlers. Serious illness may signify an underlying immune deficiency.

EBV causes most symptoms through immune modulation and can have long term consequences.

Heterophile antibody testing (Monospot) is not reliable in children under 4 years of age.

Treatment is mostly supportive.

Case Summary: NIH consulted for possible underlying immunodeficiency but all genetic testing returned normal. Patient transferred to St. Jude Children’s Hospital where she received chemotherapy with Rituxan (Rituximab) but relapsed quickly. She is currently undergoing bone marrow transplant.
References


Questions?