Viral infections of the lung, including influenza and emerging infections: histopathology

3/13/2016
Binförd-Dammin Society Companion Meeting
Atis MuehlenBachs, MD, PhD
Infectious Diseases Pathology Branch
Centers for Disease Control and Prevention

Dr. Muehlenbachs has nothing to Disclose

Outline

• Overview:
  – Viral taxonomy.
  – Patterns of disease.
• Viruses you can ‘see’ in the lung.
  – Viral inclusions and mimics.
• Selected viruses you cannot ‘see’ in the lung.
  – Bronchiolitis and asthma exacerbations.
    • Carriage versus disease.

Viral taxonomy

**Viral taxonomy: Respiratory viruses**

- Rhinoviruses (EVD68)
- Coronaviruses ([229E, HKU1, OC43, SARS, MERS])
- Bocavirus
- Adenoviruses
- CMV

**Viral taxonomy: Lung infection**

- Rhinoviruses (EVD68)
- Coronaviruses ([229E, HKU1, OC43, SARS, MERS])

**Interstitial Pneumonitis**

- Parainfluenza
- Respiratory syncytial virus (RSV)
- Human metapneumovirus
- Influenza
- Cytomegalovirus

**Bronchiolitis/bronchitis/tracheitis**

- Respiratory syncytial virus (RSV)
- Parainfluenza
- Influenza
- Rhinovirus
- Human metapneumovirus
Necrotizing inflammation

Diffuse alveolar damage

Syncytial cells and inclusions

Bacterial Bronchopneumonia

Influenza

Adenovirus
Herpesviruses 1-3 (HSV 1&2, VZV)

Influenza (H1N1)
SARS/MERS
Hantavirus
Other viruses after prolonged disease course

RSV
Parainfluenza
Measles
Nipah

Courtesy Jana Ritter/Kelly Keating, CDC
Pulmonary edema

Viral Inclusions

- Paracrystalline arrays of virions; these have light scattering properties.
- Arrays need to be large enough to be seen on an H&E stained slide.

Viral taxonomy: inclusions

Case #1

- 21 year old woman with shortness of breath, chest pain and light headedness. Mid-May.
- Emergency department: no pulmonary embolism, Lung imaging normal.
- Discharged and died.
- Autopsy: Pericarditis and pneumonia
Case #1

• What is the diagnosis?

Case #1 Diagnosis

• Lung: Negative adenovirus IHC and PCR
• Pericardium: Positive parvovirus B19 by PCR

Circulating megakaryocytes

Degenerating cells

Adenovirus

Courtesy Kelly Keating/Sherif Zaki, CDC
Adenovirus

Adenovirus

Difficult case

CMV-effect described in 1904


Cytomegalovirus

Courtesy Wun-Ju Shieh/Sherif Zaki, CDC
Paramyxoviruses

- Pulmonary findings: Bronchiolitis, pneumonitis and pneumonia.
- Syncytial cells with viral inclusions, both cytoplasmic and intranuclear.
  - Often not seen in positive cases of RSV and parainfluenza
- Viral fusion protein mediated fusion.
Case #2

- 7 year old girl with a history of asthma presented to Emergency department with difficulty breathing, chest pain, fever and coughing. Early April.
  - Diagnosed as asthma exacerbation, received albuterol and supportive care.
  - Improved and was sent home.
- Next morning had similar complaints, collapsed and resuscitation was unsuccessful.
Case #2

- Diagnosis: Influenza A(H3)-seasonal flu- infection in the setting of asthma.

Respiratory viruses and asthma

- Respiratory viral infections are clinically associated with asthma exacerbation and hospitalization.
- By NP swab, rhinovirus is most commonly detected, followed by RSV and influenza. Busse WW et al, Lancet 2010
- Question of carriage versus disease:
  - Many respiratory viruses can be present in upper airways but not lower airways.
- Immunohistochemistry can localize viral antigen to bronchioles.
Case #3

- 8 month old infant, previously well, discovered unresponsive on recliner. December.
- Resuscitation resulted in hypoxic-ischemic encephalopathy. Following a negative septic, genetic and metabolic work up, life support was withdrawn, and died 2 days after admission. NP swab was negative.

Rhinoviruses and bronchiolitis

- Following RSV (50-80%), rhinoviruses are second most detected viruses (5-25%) in NP swabs from children hospitalized with bronchiolitis. Meissner, NEJM, 2010
- Peak activity in autumn and spring.
- Severe disease seen largely in age less than 2 years (clinical immunity rapidly gained due to high exposure).
- Severe episodes associated with asthma later in life.
- Often thought to be restricted to upper airways, involvement of lower airways demonstrated by pre- and post- inoculation bronchial biopsies of human volunteers. Papadopoulos NG et al JID 2000.
- Question of carriage versus disease:
  - Prevalence of rhinovirus can be as high as 50% in asymptomatic populations.
- Immunohistochemistry can localize viral antigen to bronchioles.
Case #4

- 4 year old girl, near absent medical care, and on no medication. Cough, wheezing, shortness of breath noted late August 2014. She died two days later without medical care.
- Autopsy: asthma.
Case #4

- *Post mortem* NP swab:
  - Flu A/B, RSV, paraflu, adeno PCR NEGATIVE
  - Both rhinovirus and enterovirus PCR POSITIVE

- PCR from formalin fixed paraffin embedded tissues:
  - Positive for EV-D68

Enterovirus D68

- Outbreak in 2014.
- 1,153 people in 49 states had respiratory illness caused by EV-D68. Almost all of the confirmed cases were children, many whom had asthma or a history of wheezing.
- Likely millions of asymptomatic or minimally symptomatic cases.
- 14 confirmed deaths.

http://www.cdc.gov/non-polio-enterovirus/about/ev-d68.html
Conclusions: Respiratory viruses, bronchiolitis and asthma

- Respiratory viruses can cause bronchiolitis and asthma exacerbations.
- Significant cause of morbidity and hospitalization in the U.S.
- Limitations in understanding pathogenesis because detection is largely based on nasopharyngeal secretions.
  - Carriage versus disease.
  - Upper versus lower airways.
- Pathologic studies, including immunohistochemistry to localize antigen, can provide insight to pathogenesis.

Acknowledgements

- Infectious Diseases Pathology Branch, CDC
  - Wun-Ju Shieh
  - Sherif Zaki
  - Amy Denison
  - Kelly Keating
  - Jana Ritter