AP112 Pathologic Diagnosis of Infectious Diseases: New Strategies and Challenges

Course Director
Sherif R. Zaki, M.D., Ph.D.
Course Objectives

• Differentiate between infectious and non-infectious processes
• Design syndromic approach to diagnosis of infectious diseases
• Compare histopathologic, special stains, immunohistochemical testing and molecular methods and make a rational decision on which methods to use in your practice
Course Objectives

• Decide which criteria/tests (histopathology, special stains, IHC, etc) are applicable to achieve specific diagnoses
• Determine if testing can be performed in your laboratory vs. specialty laboratory
• Discuss clinical history, pathologic examination and epidemiologic analysis that might prompt consideration of a bioterrorism event or of an emerging disease
Agenda

• Sherif Zaki, M.D., Ph.D. 1:35-2:15
  Chief, Infectious Disease Pathology
  Centers for Disease Control and Prevention
  Role of Pathology in Studies of Emerging Infectious Diseases and Other Health Threats

• Margie A. Scott, M.D. 2:15-3:00
  Chief, Pathology & Laboratory Medicine Service
  Central Arkansas Veterans Healthcare System
  Microbiology and Molecular Applications for the Modern Laboratory
Agenda

• A. Brian West MD, FRCPPath . 3:30-4:15
  *Department of Pathology*
  *New York University Medical Center*
  *Gastrointestinal Infections: a systematic approach to diagnosis*

• Wun-Ju Shieh, M.D., M.P.H., Ph.D. 4:15-5:00
  *Staff Pathologist, Infectious Disease Pathology*
  *Centers for Disease Control and Prevention*
  *Pathologic Diagnosis of Encephalitis*
Deaths by Cause, World-Wide, 1993

Number (Millions)

- Infectious & Parasitic Diseases
- Cardiovascular Diseases
- Cancer
- Perinatal and Neonatal Causes
- Chronic Obstructive Pulmonary Diseases
- Maternal Causes
- Other Causes

Factors in the Emergence of Infectious Diseases

- Human demographics and behavior
- Technology and Industry
- Economic development and land use
- International travel and commerce
- Microbial adaptation and change
- Breakdown of public health measures
- Deliberate dissemination

From Institute of Medicine, 1992
Infectious Disease Pathology and Public Health

• Pathologists among first health care workers to encounter infectious disease outbreaks
• Pathologists are in excellent position to discover emerging infectious diseases
• Collaborative research
  – Epidemiologists
  – Clinicians
  – Veterinarians
  – Microbiologists
Infectious Disease Pathology and Public Health

• Many examples of recent emerging infectious diseases diagnosed through autopsies
• Autopsy is increasingly being viewed as an effective surveillance tool
  – Pathologic specimens can serve as sentinel indicators of emerging pathogens
Recent Global Challenges to Public Health (CDC)

- 93 - Hantavirus Pulmonary Syndrome – U.S.
- 94 - Plague/leptospirosis – India
- 95 - Leptospirosis – Nicaragua
- 95-01 -VHF s (Ebola, Lassa, RVF) – Africa, Asia
- 96 - Typhus – Burundi
- 97 - H5N1 Influenza – Hong Kong
- 98-99 - Enterovirus 71 - Malaysia, Taiwan
- 98 - Plague – Ecuador
- 99 - Nipah virus – Malaysia, Singapore
- 99-04 -West Nile virus – U.S.
- 00 - Rift Valley – Kenya, Saudi Arabia, Yemen
- 01 - Anthrax – U.S.
- 03 - SARS – Global
- 03 - Monkeypox – U.S.
- 03-04 - Pediatric Influenza Deaths – U.S.
- 02-04 – Emerging viral infections in transplant recipients – U.S.
Syndromic Approach to Diagnosis of Emerging Infectious Diseases

- Hemorrhagic Fevers – Hantavirus, Lassa, Malaria, Anthrax
- Cutaneous Rash – Monkeypox, Rickettsialpox
- Pneumonia – SARS, influenza
- Encephalitis – WNV, Nipah
- Transplant (Immunosuppressed) – WNV, LCM, Rabies
Syndromic Approach to Diagnosis of Emerging Infectious Diseases

• Histopathologic pattern
• Laboratory approach
  – Culture
  – Serology
  – EM
  – IHC
  – Molecular
Background: Organ Transplants

U.S. Transplants Performed, 2001*
N=24,123

*Organ Procurement and Transplantation Network
Organ and Tissue Recovery

Donor

Screening and Testing

Organs

Eyes, Skin

Tissues

Heart
Lungs
Liver
Pancreas
Kidney
Vascular
Bone
Musculo-Skeletal

Eyes
Skin

Organ and Tissue Recovery

Donor

Screening and Testing

Organs

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Heart
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Kidney
Vascular
Bone
Musculo-Skeletal

Eyes
Skin

Investigation of Rabies Infections in Organ Donor and Transplant Recipients — Alabama, Arkansas, Oklahoma, and Texas, 2004

On July 1, this report was posted as an MMWR Dispatch on the MMWR website (http://www.cdc.gov/mmwr).
Case Histories

• On Dec 8, 2003, CDC contacted by WI DOH
  – Two organ transplant recipients died
  – Another organ transplant recipient with seizure
  – All from same donor

• Organ procurement organization contacted, all stored tissues quarantined
EM of Cytopathic Agent in Vero E6 Cells
Kidney recipient #1
Kidney recipient #2: skin
Liver recipient
Imported Lassa fever – New Jersey. MMWR, 2004; In Press.
Clinical History

• 38 yo male from NJ
• Traveled to West Africa frequently
• 08/21/04 – high fever, chills, severe sore throat, diarrhea, and back pain
• 08/23/04 – boarded flight from Sierra Leone to Newark, connecting at Gatwick Airport
• 08/24/04 – arrived in Newark, was hospitalized, and died
Geographic Distribution of Arenaviruses
## Airplane Seating Plan

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- **Red** – Index case
- **Green** – contacted and healthy
- **Blue** – not contacted

Imported Lassa fever – New Jersey. MMWR, 2004; In Press.
• 36 yo male 3rd mate on MS Overseas Marilyn

• Made port in West Africa (Sierra Leone, and Nigeria)

• 08/23/04 – high fever, chills, severe sore throat, and myalgia

• 08/31/04 – died onboard, body frozen in meat locker, and ship quarantined off of Texas coast
Dengue

May 1993

On presentation

3 days later
<table>
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Hantavirus Pulmonary Syndrome Cases by Outcome United States, as of January 15, 2003

*Thirty-two additional cases (nineteen deceased) with onset before 1993 not shown.*

*N=333*
Rainfall Data 1994 - 1998, Springfield, IL

Month

Precipitation (inches)

1998 Precipitation (inches)  1994-1997 Mean Precip. (inches)

Illinois triathlon
Springfield Triathlon Participants
(n=875)
Recognition: Palm Beach County, Florida

- 63 yo male photo editor employed by American Media, Inc.
- Onset 9/30/01: fever, fatigue, sweats, altered mental status
- Admitted to hospital 10/2
- CDC notification 10/3
Inhalational Anthrax

CSF Gram Stain

Chest CT
Autopsy on suspect cases of anthrax

- Risks
- Standard precautions
- Minimize aerosols and environmental contamination
- Avoid embalming, cremation preferred

Inhalational Anthrax: Florida 2001

Index Case in New York City

- 38 year old F; works at NBC
- Sept 25th: Onset of ulcerative skin lesion on chest

Index Case in New York City

- **Oct 1\(^{st}\):** Seen by Infectious Disease MD and reports handling “threat” letter at work
- **Oct 3\(^{rd}\):** Bacterial cultures of wound and Sept 25th letter test (-) for *B. anthracis*
- **Oct 8\(^{th}\):** Patient re-contacts DOH after hearing of Florida anthrax case
- **Oct 9-11:** Developed contingency plans with NBC
Index Case in New York City

Friday, October 12, 2001

- 12 AM: CDC reports (-) PCR on biopsy
- 3 AM: CDC reports IHC + on biopsy
- 6 AM: NYCDOH’s EOC activated
- 9 AM: NBC informed. Start epi investigation
- 12 PM: Press conference at NBC
- 3 PM: Open antibiotic distribution clinic
Index Case in New York City
Friday, October 12, 2001

- 4 PM: 2nd “threat” letter (dated 9/18) found
- 11 PM: 2nd letter tests (+)
When it rains it pours....

• By the evening of October 12th, 3 additional highly suspect cutaneous cases were reported (all associated with major media outlets)
• As each case confirmed by IHC, multidisciplinary teams mobilized for on-site investigations and response
Epidemiologic Investigations of Cases

1. Palm Beach County – 10/3
2. New York City – 10/12
3. Washington, DC – 10/15
4. Trenton, NJ – 10/17
Cases of anthrax associated with paths of mailed envelopes and intended target sites.

- Hamilton, NJ Postal Facility:
  - Mail Carrier, NJ
  - Bookkeeper, NJ
  - Hospital Worker, NYC
  - Elderly Woman, CT
- Morgan, NYC Postal Facility:
  - State Dept, VA Mail Processing Facility
- West Palm, FL Postal Facility
- Brentwood, DC Postal Facility
- Daschle Office
- Leahy Office**

- Cutaneous case
- Inhalational case
- Intended target
- Known path of mailed envelopes
- Presumed or intended path of mailed envelopes
- Uncertain path of contaminated mail
- Recovery site of implicated envelope

- Blue = Sept 18 envelopes
- Green = Oct 9 envelopes
- Orange = Undetermined exposure to envelopes
Spider Bite
(brown recluse)
Poxviruses - EM

Variola virus
Vaccinia virus
Monkeypox virus
Tanapox virus
Milker’s nodule virus


Case 4: 7 yo Asian male, Anshun, China, admitted 7 April 1945, died 8 April 1945. Refugee child to US Army Hospital.

Child: Secondary lesions 5/27/03, adjacent to primary inoculation site on left hand.
Initial Signs of a Worldwide Outbreak

Nov, 2002
Cases of pneumonia were circulating in China’s Guangdong province.

Feb 10-11, 2003
A report on ProMed describes the problem. China reports to WHO that an outbreak of highly infectious pneumonia of unknown etiology has resulted in 305 cases, including 5 deaths, since November 16, 2002.

February 26, 2003
WHO official (Dr. Carlos Urbani) working in Hanoi notifies WHO of unusual disease in a patient.

March 12, 2003
WHO issues global health alert about cases of atypical pneumonia in Hong Kong and Vietnam.
Chain of transmission among guests at Hotel M—Hong Kong, 2003

Data as of 3/28/03

* Health-care workers; † All guests except G and K stayed on the 9th floor of the hotel. Guest G stayed on the 14th floor, and Guest K stayed on the 11th floor; § Guests L and M (spouses) were not at Hotel M during the same times as index Guest A but were at the hotel during the same times as Guests G, H, and I, who were ill during this period.
SARS Coronavirus Isolate

Coronavirus-infected cell in Bronchial Alveolar Lavage (BAL) of SARS Patient

SARS-CoV in Intraalveolar Fibrin

2003-04 Influenza Season

• Early onset
  – Early reports of pediatric deaths
• Increased media attention
• H3N2 predominant strain
• Mismatch of vaccine and circulating strain
• CDC requested reporting of influenza-associated deaths
Domestic Influenza Activity – Pediatric Impact

N = 135 deaths from 38 states

Date of Death
Influenza A (H3N2) Fujian-like

Number of Deaths
## Signs and Symptoms (n=135)

<table>
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<tr>
<th>Percentage</th>
<th># children</th>
<th>Sign/symptom</th>
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<tbody>
<tr>
<td>77%</td>
<td>104</td>
<td>Fever/ feverishness</td>
</tr>
<tr>
<td>59%</td>
<td>80</td>
<td>Cough</td>
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<td>48%</td>
<td>65</td>
<td>Difficulty breathing</td>
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<td>37%</td>
<td>50</td>
<td>Runny nose/congestion</td>
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<td>30%</td>
<td>40</td>
<td>Vomiting</td>
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<tr>
<td>14%</td>
<td>19</td>
<td>Seizures</td>
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<tr>
<td>11%</td>
<td>15</td>
<td>Diarrhea</td>
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Children experienced > one symptom
Laboratory confirmation* (n=135)

- 41 (30%) Viral culture
- 82 (61%) Rapid tests
  - 35 (43%) were confirmed by a second method
- 23 (17%) Direct Fluorescent antibody
- 18 (13%) IHC staining**
- 4 (3%) PCR

* Some children were tested by > 1 method
** 6 diagnosed by IHC alone
Pandemic Influenza: The Ever Present Threat
Direct Interspecies Transmission of Avian Viruses to Humans Exposed to Infected Poultry

- 1997: 18 cases of human respiratory illness caused by HP avian H5N1; 6 deaths – Hong Kong
- 1998/9: 8 cases of human respiratory illness caused by H9N2; no deaths – China, HK
- 2003: 2 additional HP H5N1 cases in humans; 1 death – China, HK
- 2003: >80 cases of infection by HP H7N7 avian viruses; 1 death - ND
- 2004: 28 cases of human respiratory illness by HP H5N1 avian viruses; 20 deaths – Vietnam and Thailand
Summary

- Era of increased awareness of emerging and reemerging diseases
- Fundamental principle is recognition of these diseases
- Importance of multidisciplinary approach
- Importance of syndromic approach
- Importance of traditional laboratory and contemporary methods
- Frontline role of pathology
  - Recognition of emerging infectious diseases
  - Guiding epidemiologic investigations
  - BT investigations