Diagnostic Challenges in Infectious Disease Pathology

Gary W. Procop, MD
Chair, Clinical Pathology
Staff, Anatomic Pathology
Director, Molecular Microbiology, Mycology and Parasitology
Cleveland Clinic

Case #1

- This is a 43 yr old woman with mediastinal adenopathy & scattered small peripheral pulmonary nodules.
- H&E's show dense hyalinized fibrous tissue with small foci of necrosis and peripheral, poorly defined noncaseating granulomas.
- I really though this was going to be burnt-out sarcoid, but the special stains show these pleomorphic and football shaped yeast that I think are too big for Histo, and the shape is unusual for crypto.
- They stain a peculiar dark red-brown in the AFB stain, and seem to have a halo or capsule.
- Cultures are pending, but I'm skeptical that anything will grow. Sampling might be a problem as the yeast were not seen in the Calcufluor stain made from the tissue submitted for culture.
- Your Opinion, please?

GMS

AFB
Hamazaki-Wesenberg Bodies

- AKA
  - Yellow-brown bodies, chromogenic bodies, elliptical bodies and Hamazaki corpuscles.
- Commonly associated with Sarcoidosis
- May be mistaken for the “cigar bodies” of *Sporothrix schenckii*.

Cas # 2

- 52 year old Male
- Government employee
- Biologic weapons detoxification
- Soviet Union / Kazakhstan
- CLL
- Immunosuppressive Therapy
- Mental Status Changes -> Brain Biopsy
Different patient, similar presentation

Thoughts, Thoughts,
Comments, Comments,
Questions, Questions,
Diagnosis?

Chronic Granulomatous Meningoencephalitis

- Chronic Granulomatous Meningoencephalitis vs. Primary Amebic Meningoencephalitis

- Differentiation of Free-Living Amoebae
  - *Naegleria fowleri*, *Acanthamoeba* sp., and *Balamuthia mandrillaris*.
### Disease Differences

<table>
<thead>
<tr>
<th>Disease</th>
<th>Details</th>
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</table>
| Chronic Granulomatous Meningoencephalitis | - Pts with immunodef/ chronic disease.  
- Insidious onset: weeks/months.  |
| Primary Amebic Meningoencephalitis | - Pts with fresh water exposure.  
- Acute onset: days  
- Rapidly fatal. |

### Parasite and Histopathology Differences

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Details</th>
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</table>
| CGM                             | - Granulomas/mononuclear cell response  
- Perivascular: Cysts and trophozoites  
  - Thick, undulating cyst wall – easily recognized.  
  - Acanthamoeba and Balamuthia cannot be differentiated by morphology – CDC uses genus-specific PCR.  |
| PAM                             | - Hemorrhagic necrosis and neutrophils  
- Perivascular: Trophozoites only |

### Case #3

- 39-year old woman from Kentucky with a past medical history significant for migraine headaches.
- The patient presented to a local emergency department with the acute onset of headache, altered mental status and neck pain.
- Symptoms were preceded two weeks earlier by a pruritic migratory rash.
- Antibiotic therapy was initiated and she was admitted for probable meningitis.
- Seizure prompted additional workup, including:  
  - lumbar puncture,  
  - magnetic resonance imaging (MRI),  
  - electroencephalogram (EEG) and  
  - cerebral angiography;  
  - the results of these yielded no specific diagnostic abnormalities.
- A right temporal lobe biopsy was performed which was reported to contain chronic active meningoencephalitis with focal chronic granulomatous vasculitis.
- Differential diagnostic considerations included Varicella-Zoster viral infection and primary central nervous system (CNS) vasculitis.
Cyclophosphamide, prednisone and anti-epileptic therapy was initiated.

Her mental status gradually improved over 2 weeks but she then suffered an abrupt decline in responsiveness with development of fever and leukocytosis.

MRI showed multiple, bilateral contrast enhancing lesions throughout the brain, which were suggestive of progressive disease.

A lumbar puncture showed an elevated white blood cell count with lymphocytic pleocytosis and high protein content consistent with CNS vasculitis.

Extensive cerebrospinal fluid tests in search of an infectious cause were performed and were negative.

The patient developed respiratory failure and died, 10 weeks after initial presentation.

A complete autopsy with evaluation of the brain was performed.

Neuropathologic Findings

Grossly, mild diffuse cerebral edema was present

Microscopic examination demonstrated an extensive inflammatory process involving the parenchyma, meninges and ventricular system in a predominantly perivascular pattern.

Necrotic foci and hemosiderin were present at the site of prior surgical instrumentation, with evidence of regenerative proliferation.
- Viral inclusions were absent.
- There was no evidence of systemic vasculitis.
- Nematode worms were present in the brain associated with the inflammatory infiltrates.
- Nematodes were not present in any of the other organs and systemic vasculitis was absent.
Thoughts, Thoughts,
Comments, Comments,
Questions, Questions,
Diagnosis?

Corpus Isthmus Bulb
Diagnosis:

Fatal Meningoencephalitis caused by *Halicephalobus deletrix*

- *Halicephalobiasis* is a helminthic infection caused by the genus *Halicephalobus*, a free-living soil saprophyte.
- Halicephalobic infection is intermittently encountered in horses and causes tissue destruction and granulomatous lesions that most commonly affect:
  - central nervous system, skin and kidneys.
  - Other varied manifestations have included nasal tumor involvement, osteomyelitis, granulomatous prepuce infection, granulomatous nephritis, meningoencephalitis, and occasionally disseminated disease.

- Several equine cases involving the central nervous system have presented with ataxia, all of which culminated in euthanasia or death by overwhelming infection.
- Postulated route of entry in horses is penetration of skin and mucous membranes by the free-living soil nematode with invasion of other adjacent organs including bone and sinuses followed by hematogenous spread.
- This is the fourth human with an infection caused by *Halicephalobus*

- The free-living form of *Halicephalobus* appears to enter its host through a break in the skin or oral cavity.
- It invades and replicate parthenogenetically within mammalian tissue with a predilection for the CNS where it provokes a brisk inflammatory response, resulting in progressive mental confusion, lethargy and death.
- Previous patients with these infections also had brain involvement and infections were uniformly fatal.
Epidemiologic Associations:
- Traumatic farming accident which resulted in extensive lacerations and considerable wound contamination with manure.
- A patient admitted with leg pain and mental confusion and died 18 days later; the mechanism of infection is unknown.
  - That patient was a small ranch owner on which a few horses were stabled, but he had little to no contact with them.
- The third fatal infection occurred to a man who was clinically debilitated and possibly acquired the infection from decubitus ulcers.
- Current patient: No horse contact, but lived in Kentucky, scraped knee and tended a Koi pond.

Helminthic DDX
- **Strongyloides stercoralis** – as part of a hyperinfection syndrome;
  - Filariform larvae in tissue, not rhabditiform as present here; should also be in GI tract and lungs.
- **Toxocara** species or less commonly **Baylisascaris** species – as agents of visceral larva migrans;
  - Contain lateral alae.
- CNS helminths, such as **Angiostrongylus** and **Gnathostoma** species.
  - Are large, adult-sized worms, amongst other features.

What do Michigan and Oklahoma have in common? Pts 4, 5, and 6

**Oklahoma: Pt 4**
- 21 year old previously hthy man, potentially exposed to chemicals, with recurrent hemoptysis.

**Michigan: Pt 5**
- 18 y/o man with
  - Watery diarrhea; tachypnea with bilateral pleural effusions, recurrent -> two pleurectomy procedures

**Oklahoma: Pt 6**

Oklahoma: Patient 6

- A previously healthy 35-year-old man, without a history of international travel, consulted his primary care physician for “coughing up reddish material.”

- At the time of presentation, the patient was thought to have a right-sided spontaneous pneumothorax.

- The patient had a persistent cough for another year. A CT scan of the chest demonstrated a cavitary mass lesion in the right lower lobe.

- The cough persisted; two consecutive rightsided pneumothoraces occurred, which were accompanied by a right-sided pleural effusion and marked leukocytosis.

- The placement of a chest tube and thoracostomy resulted in 800 mL of brown fluid.

- No organisms were seen on Gram stain, acid-fast stain, or direct examination for fungal elements. The corresponding bacterial, mycobacterial, and fungal cultures were negative.

- The patient complained of dyspnea and underwent a right thoracoscopy. Moderate pleural peel throughout the lung with dense adhesions between the visceral and parietal pleura.

- An anterolateral thoracotomy was required to remove the pleural peel, and a pleurodesis with talc was performed.

- The pleurectomy specimen was sent to surgical pathology for histopathologic analysis. Abundant circular to oval structures were seen, thought to possible represent *Coccidioides*. These were birefringent.

Oklahoma: Pt 4 : BAL
North American Paragonimiasis

<table>
<thead>
<tr>
<th>Paragonimus species</th>
<th>Endemic Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. westermani</em></td>
<td>Asia, India, Philippines, New Guinea</td>
</tr>
<tr>
<td><em>P. miyazakii</em>¹</td>
<td>Japan</td>
</tr>
<tr>
<td><em>P. skrjabini</em></td>
<td>China and Southeast Asia</td>
</tr>
<tr>
<td><em>P. heterotremus</em></td>
<td>Thailand, China, Southeast Asia</td>
</tr>
<tr>
<td><em>P. hueitungensis</em>²</td>
<td>China</td>
</tr>
<tr>
<td><em>P. uterobilateralis</em></td>
<td>West Africa</td>
</tr>
<tr>
<td><em>P. africanus</em></td>
<td>West Africa</td>
</tr>
<tr>
<td><em>P. kellicottii</em></td>
<td>North America</td>
</tr>
<tr>
<td><em>P. mexicanus</em></td>
<td>Central and South America</td>
</tr>
</tbody>
</table>

1. Blair et al suggests the *P. miyazakii* is likely a subspecies of *P. skrjabini* based on molecular comparative analyses.  
2. Some contend that *P. hueitungensis* is synonymous with *P. skrjabini*.

Most Common Signs and Symptoms

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Average Frequency</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>83%</td>
<td>62%-100%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>70%</td>
<td>61%-95%</td>
</tr>
<tr>
<td>Chest pain or Discomfort</td>
<td>65%</td>
<td>38%-94%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>42%</td>
<td>5%-53%</td>
</tr>
<tr>
<td>Fever and/or Chills</td>
<td>37%</td>
<td>11%-67%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2%</td>
<td>0%-8%</td>
</tr>
</tbody>
</table>

Thoughts,
Comments,
Questions,
Diagnosis?
### Radiographic Feature
- Average Frequency (Number with Finding / Number Examined for Finding)
- Range

<table>
<thead>
<tr>
<th>Radiographic Feature</th>
<th>Average Frequency</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>58% (123/211)</td>
<td>52%-68%</td>
</tr>
<tr>
<td>Pleural Effusions</td>
<td>51% (108/211)</td>
<td>10%-66%</td>
</tr>
<tr>
<td>Cystic Lesions</td>
<td>32% (67/211)</td>
<td>13%-46%</td>
</tr>
<tr>
<td>Linear Streaks</td>
<td>25% (53/211)</td>
<td>3%-41%</td>
</tr>
<tr>
<td>Nodules</td>
<td>20% (43/211)</td>
<td>8%-25%</td>
</tr>
<tr>
<td>Pleural Thickening</td>
<td>16% (33/211)</td>
<td>7%-28%</td>
</tr>
<tr>
<td>Ring Shadow</td>
<td>14% (19/135)</td>
<td>3%-23%</td>
</tr>
<tr>
<td>Calcified Lesions</td>
<td>6% (4/64)</td>
<td>4%-8%</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>3% (1/39)</td>
<td>Not available; only a single study reported on adenopathy.</td>
</tr>
<tr>
<td>Normal</td>
<td>8% (11/140)</td>
<td>5%-13%</td>
</tr>
</tbody>
</table>

### Parasite Egg Morphology
- Important features: egg size, the location of greatest width with respect to the diameter of the egg, the presence of abopercular thickening, and the character of the egg shell (i.e. smooth vs. pitted or dimpled).

- **P. kellicotti**: average 91.22 +/- 3.60 µm in length [range 82.3-99.8 µm] with a mean width of 56.70 +/- 1.78 µm [range 54.3-61.3 µm].
  - The thickness of the shell average 2.27 +/- 0.26 µm in thickness [range: 1.68-2.68 µm].

- **P. mexicanus**: average 74.11 +/- 3.28 µm in length [range 64.8-78.8 µm] with a mean width of 44.45 +/- 1.97 µm [range 38.3-45.5 µm].
  - The shell thickness averages 1.17 +/- 0.19 µm [range: 0.67-1.34 µm] (127, 181).

- Important, as **P. mexicanus and P. kellicotti** have a similar egg shape (i.e. broadest centrally), which is distinctly different from **P. westermani**, which is broadest near the operculum and has more distinct abopercular thickening.

### Invasive Hyalohyphomycosis

The eggs of **P. westermani**
- measure 80 x 120 µm, but rarely exceed 80 µm in histologic sections
- are brown, ovoid, and operculate.
  - the egg tapers from the broadest aspect, which is between the central aspect (i.e. the equator) of egg and the opercular end, to the narrowest aspect near the abopercular end
  - the shell measures approximately 2 µm, except where it is thickened at the abopercular end and measures approximately 4 µm in thickness.
Most Common Causes

- Aspergillus -
  - *A. fumigatus* most common
  - Aspergillosis

- Fusarium
  - Fusariosis

- Pseudallescheria
  - Pseudallescheriosis

Less Common, but Important Causes

- Paecilomyces
- Acremonium
- Scopulariopsis

Any fungi is a potential pathogen in a sufficiently immunocompromised host.

Case 6

- 8 year old child involved in accident on a farm.
- Feces in abdominal wound
- “Fuzz” on the surface of wound.
  - Histopathology demonstrates...
Fusarium

Case #7

- 37 year old female with significant bronchiectasis
- Endoscopy revealed material in the lumen.
- Transbronchial biopsy demonstrated...
Pseudallescheria boydii

Challenges in Infectious Disease Pathology

- DDx may be limited through:
  - A knowledge of infectious diseases
  - A knowledge of microbiology
  - An attention to detail.

- Clinical and Microbiologic Correlation may provide supportive information.

Questions / Comments