Fatal Meningoencephalitis Diagnosed by Autopsy Tissue Analysis

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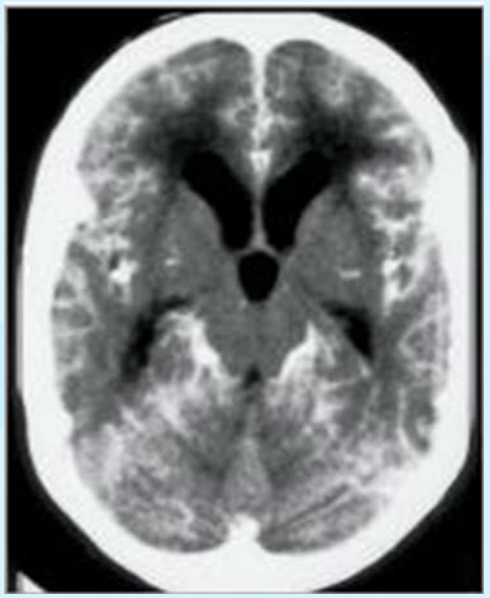
The findings and conclusions are those of the presenter and do not necessarily reflect the views of US Department of Health and Human Services or the Centers for Disease Control and Prevention

Clinical Presentation

- 09/03/2013: 55 year old woman from Texas presented to the emergency department with
  - fever
  - headache
  - nausea
  - vomiting
- A week prior - she had gone to primary care physician and ER with the same symptoms.
- She also had mental confusion and malaise this time.
- 09/03/2013: Admitted to the hospital.
- Recently traveled to Mexico – 6 weeks prior to the admission.
  Originally from Mexico – history of frequent travel.

Hospital Course and Radiologic Findings

- 09/04 to 09/08/2013
  Developed dysphagia, insomnia and agitation.
- 09/09/2013: Admitted to ICU.
  Alert to self, could respond to questions.
- 09/11/2013: Developed delirium;
  she had to be in restraints.
- Chest X-ray was unremarkable.
- CT scan chest - No consolidation or pleural effusion. No lymphadenopathy was noticed.
- CT scan brain showed cerebral edema, meningeal enhancement & hydrocephalus.



CT scan showing meningeal enhancement & hydrocephalus (Not from this patient)

Laboratory Findings

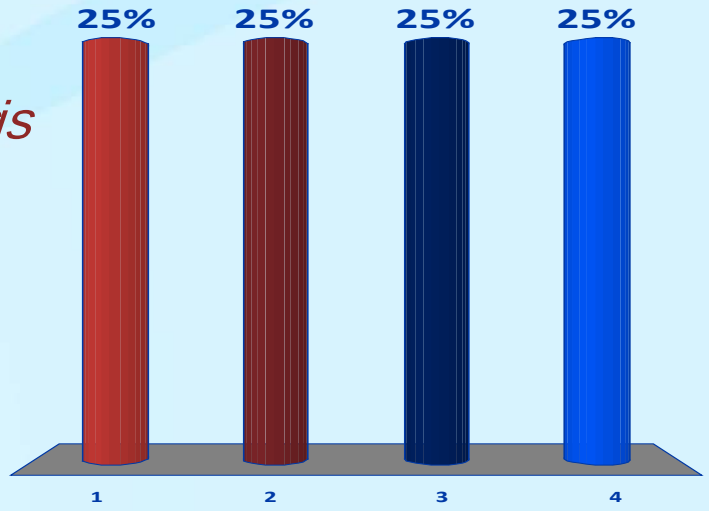
CSF Findings	
RBC	24 per µl
WBC	**472 per µl**
Neutrophils	10 %
Lymphocytes	**89 %**
Monocytes	1 %
Glucose	**29 mg/dl** ↓
Protein	**190 mg/dl** ↑

Blood and Culture Findings	
WBC count	5.5 (x10^3/µl)
Neutrophils	73.6 %
Lymphocytes	15.7 %
Monocytes	10.2 %
Glucose	126 mg/dl
Protein	8.1g/dl
CSF and blood cultures negative	

- CSF with **lymphocytic pleocytosis.**

Question 1. *What is the most likely diagnosis or pathogen responsible?*

1. West Nile virus
2. Herpes simplex virus
3. Mycobacterium
4. Rabies virus



Additional Test Results and Information

- Tested **negative** for:
  - WNV, HSV, Influenza A and B
  - Hepatitis A, B, C, and HIV
- **PPD and QuantiFERON tests for TB were negative.**
  AFB smear of CSF was negative.
- No animal bites reported in the medical records.
- 09/19/2013: Mental condition deteriorated. Shunt was placed for hydrocephalus.
- 09/29/2013: Patient pronounced dead (following 4 weeks of illness).
- 10/02/2013: Autopsy performed in a Texas facility. CNS tissues sent to the Infectious Diseases Pathology Branch, CDC – primarily for the Rabies rule-out and other evaluations.

Infectious Diseases Pathology Branch

Pathologists, molecular biologists, electron microscopists, epidemiologists

Diagnostic Approach

- Histopathologic pattern
- Clinical and epidemiologic features
- Multi-disciplinary laboratory analysis

Formalin-fixed, paraffin embedded (FFPE) biopsy and autopsy tissue

Histopathology & Immunohistochemistry Lab

- Routine and Special Stains
- Immunohistochemical (IHC) Assays (bacteria, viruses, fungi, parasites)

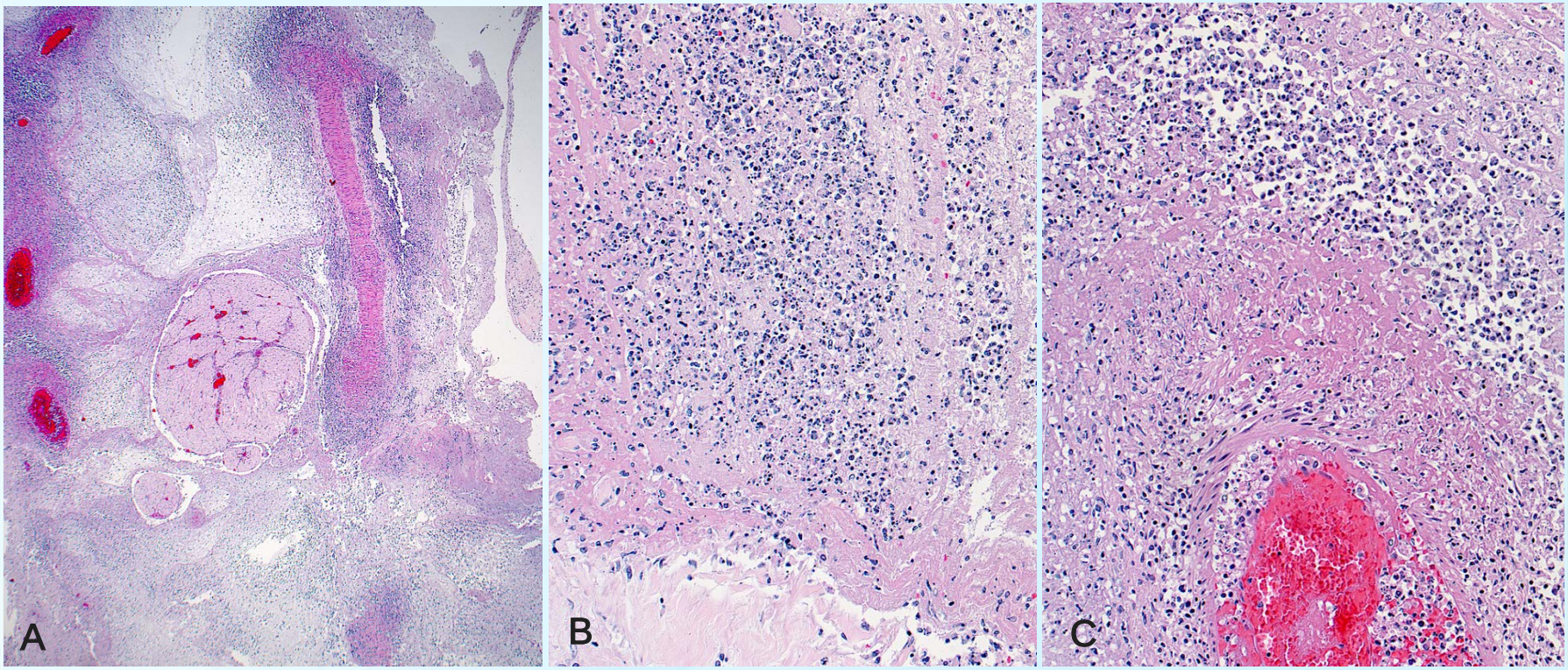
Molecular Pathology & Microbiology Lab

>120 PCR/RT-PCR Assays (bacteria, viruses, fungi, parasites) & Syndrome based panels (Myocarditis, viral respiratory infections)

- Real-time PCR/ RT-PCR Assays
- Conventional PCR/RT-PCR & Sanger Sequencing
- In development - Pyrosequencing based assays/NGS

Histopathologic Analysis (during The Shutdown)

- Sections of cerebellum, pons, medulla and midbrain showed marked edematous and inflamed leptomeninges with infiltrates (neutrophils and lymphocytes)

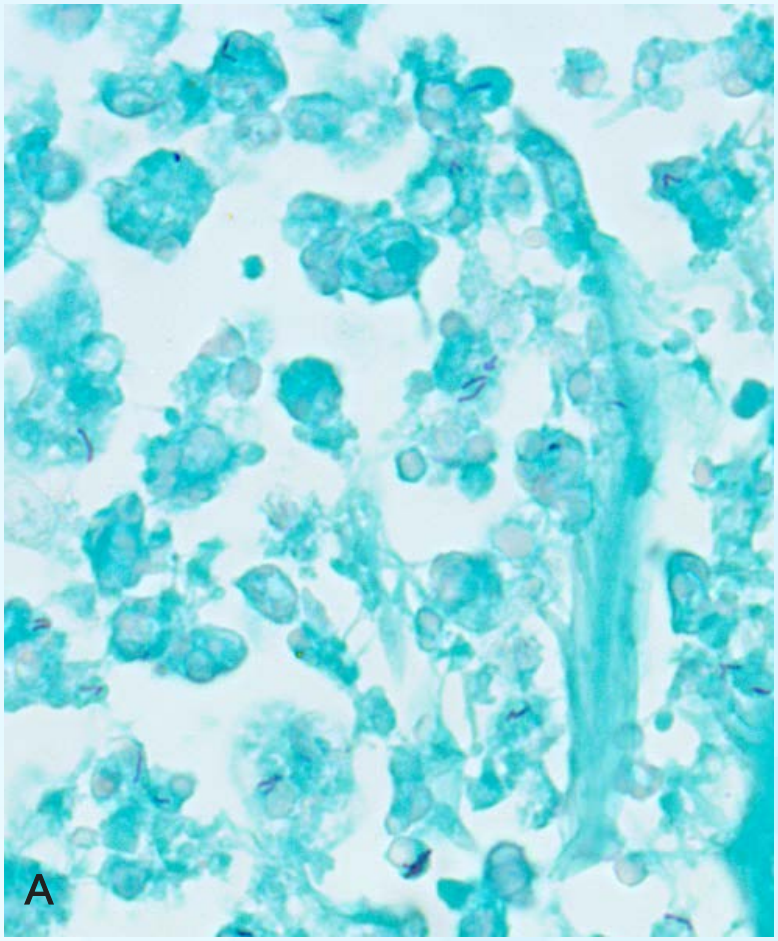


A. Leptomeninges showing acute purulent meningitis, vasculitis, edema and hemorrhage.

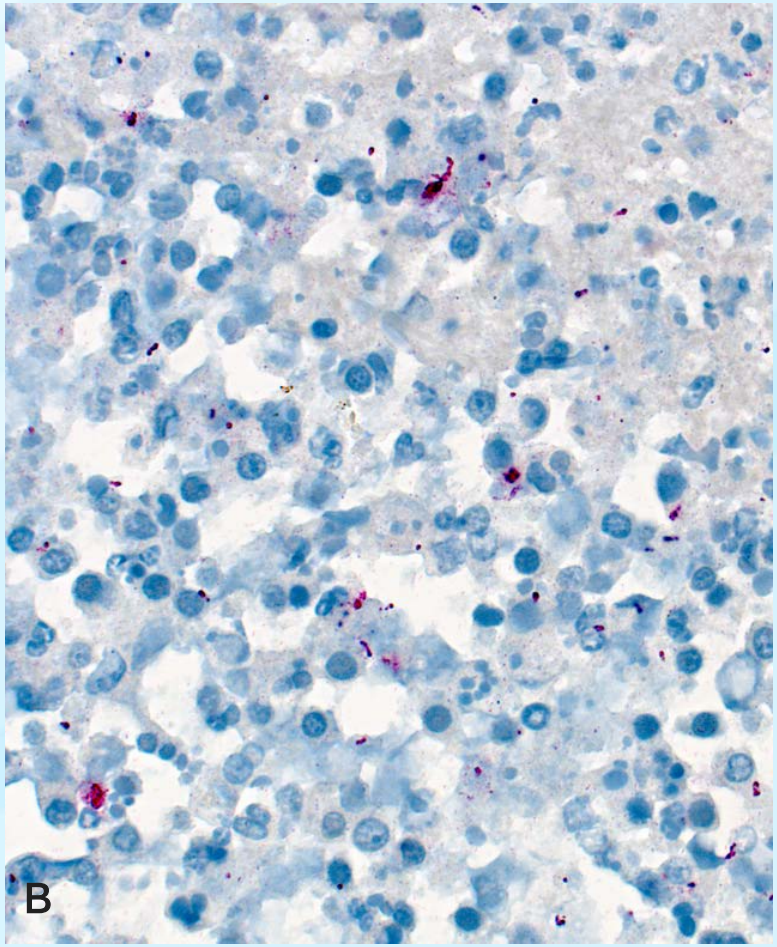
B. & C. Higher power showing acute necrotizing purulent inflammation, vascular necrosis and vasculitis. No granulomas.

- **No viral inclusions were seen in CNS. IHC for Rabies virus was negative.**

Special Stains and IHC Studies for Mycobacteria



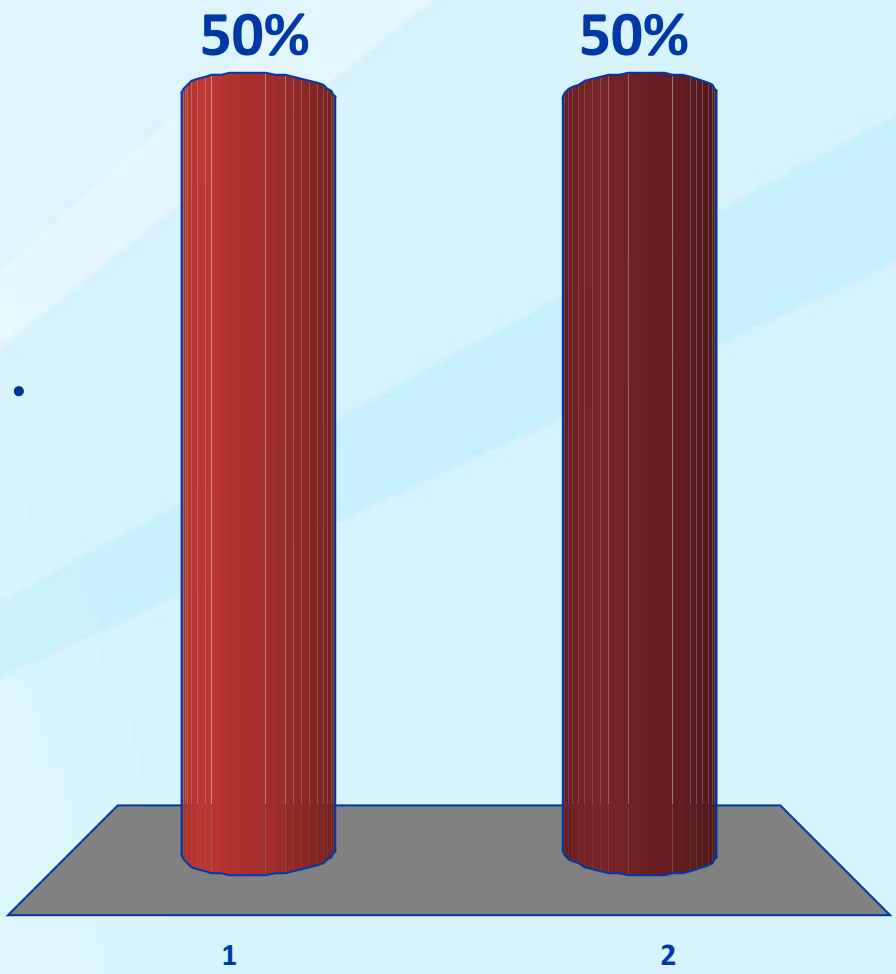
A. Acid fast bacilli seen on ZNAF stain



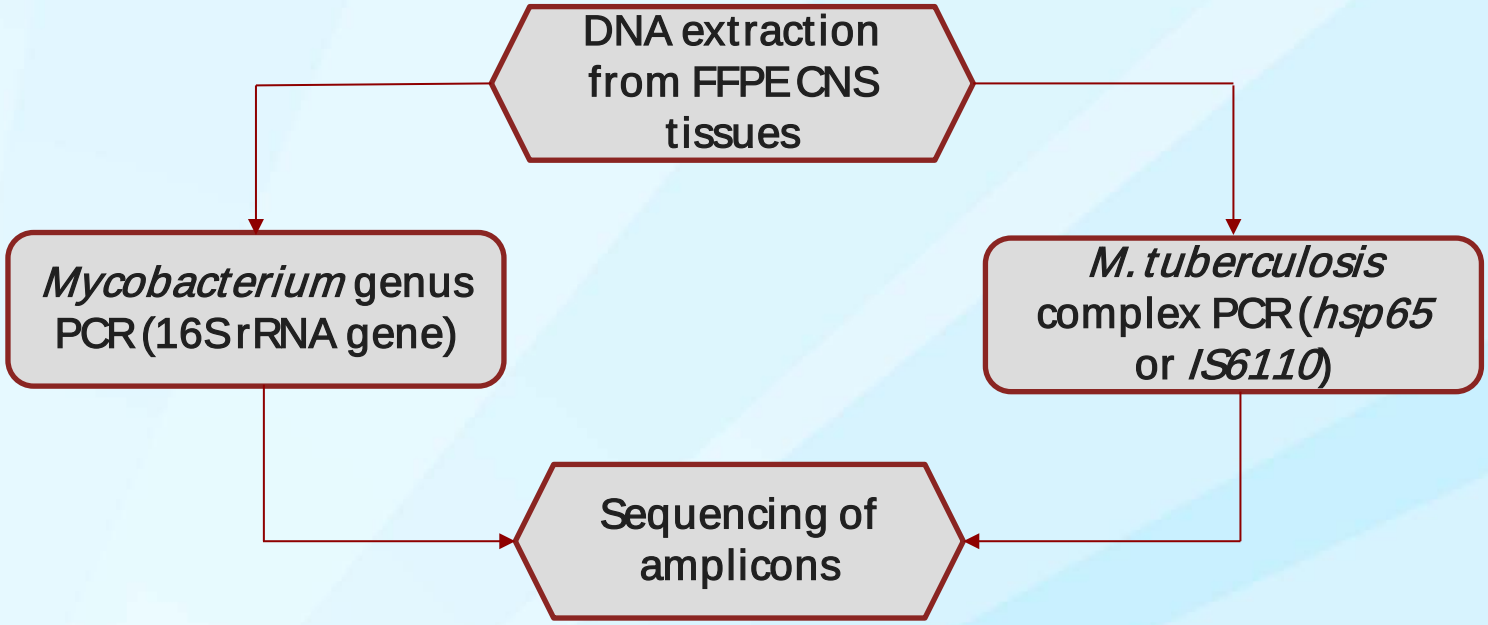
B. Mycobacterial antigens as seen by IHC

Question 2. Which one is the causative organism?

1. *M. tuberculosis* complex sp.
2. Non-tuberculous Mycobacterium sp.



Molecular Analysis of Paraffin-Embedded Tissues



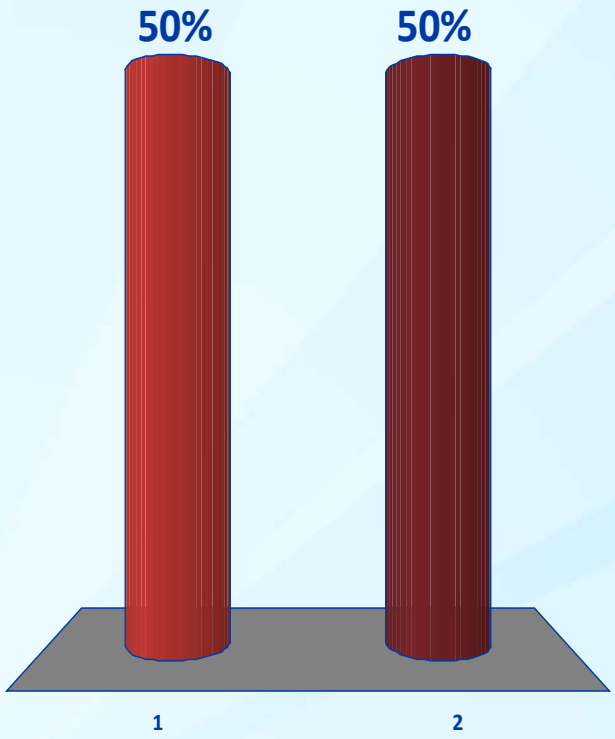
- **Both PCR assays were positive and *M. tuberculosis* complex spp. was identified by sequencing of amplicons.**

  Drug resistance?? Concerns for people who performed autopsy.

- Molecular Detection of Drug Resistance (MDDR) testing performed by TB lab - No mutations detected in genetic loci associated with drug resistance to rifampin and INH.

Question 3. *Would any contact investigation (for involved healthcare workers, other patients and contacts) be necessary?*

1. YES
2. NO

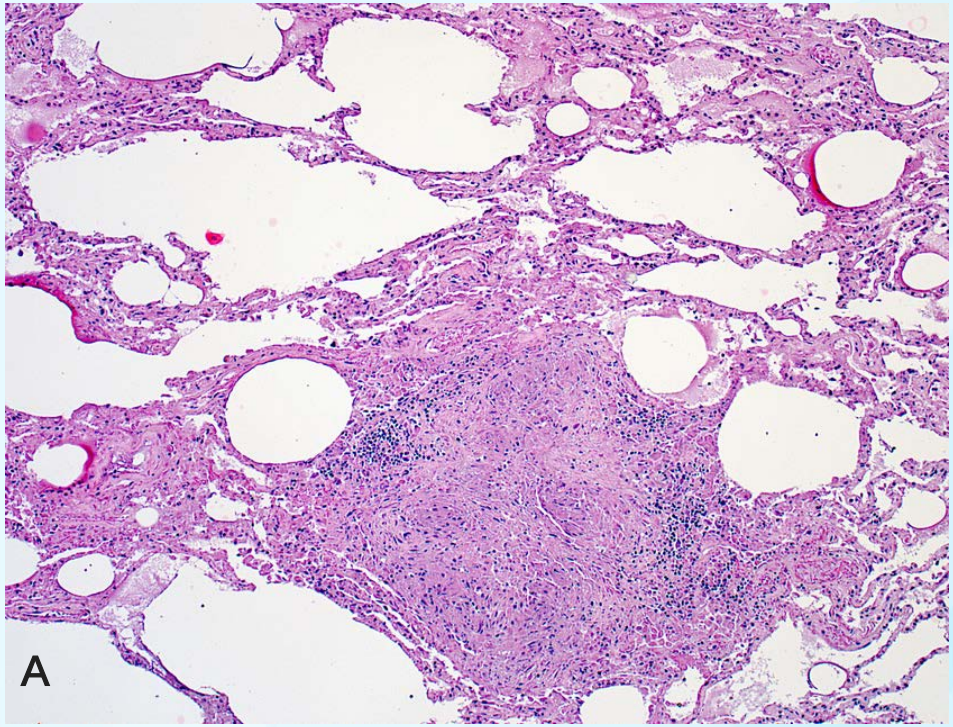


Active pulmonary disease or not?

- Additional respiratory tissues (lung, bronchus) were obtained from Texas.
- Histopathological evidence of bronchopneumonia.
- Special stains, IHC and molecular studies were performed on the respiratory tissues

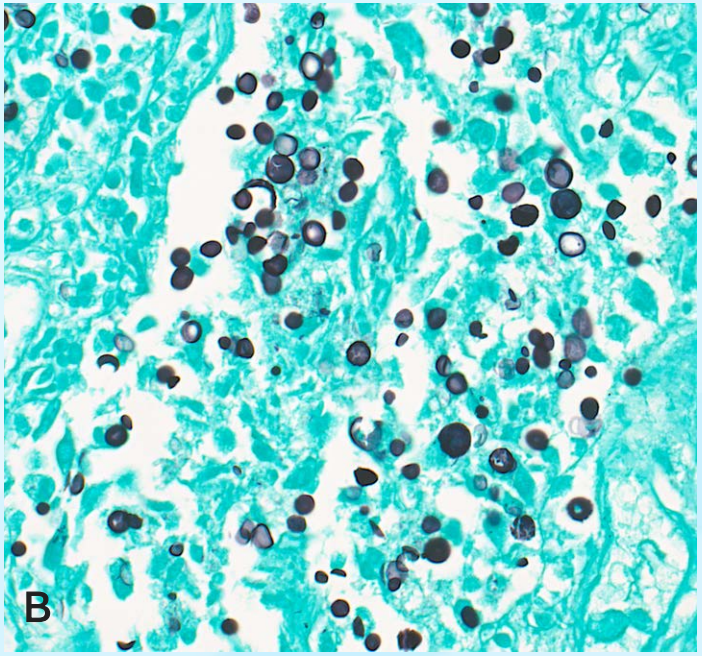
Lung tissue analysis

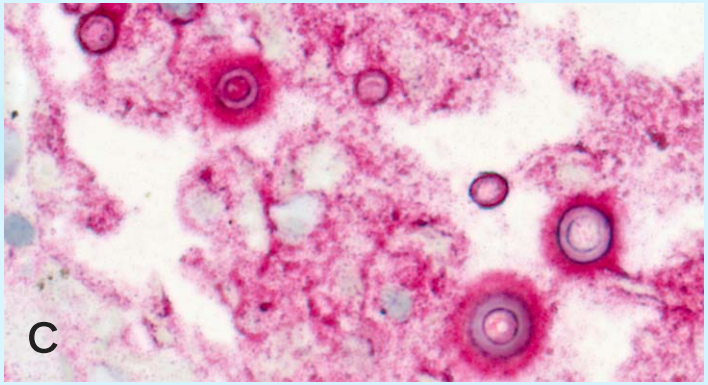
- No molecular evidence of Mycobacteria in respiratory tissue.



A: Lung showing scattered non-caseating granulomas. No acid fast bacilli or IHC staining for mycobacteria seen.

- CNS tissues were negative for Cryptococcus.





B: GMS stain showing pleomorphic budding fungal forms.
C: Cryptococcal IHC stain.

Conclusions and Lessons Learned from the Case

- Tuberculous meningitis is the most severe form of infection caused by *M. tuberculosis*, causing death or disability in more than half of those affected.

- Rapid recognition is crucial. Delays in initiating treatment are associated with poor outcome.

  - Patients in Stage I: 19% mortality; Stage III: 69% mortality
  - **Don't delay therapy if suspicious of TB meningitis**

- The diagnosis is challenging due to non-specific symptoms and may mimic other causes of meningoencephalitis.

- Diagnosis is also hampered by the low sensitivity of CSF microscopy and the slow growth of *M. tuberculosis* in conventional culture systems.

Some important features generally associated with the disease

CSF Findings	Radiologic Findings	Pathologic Findings
Lymphocytic pleocytosis	Basal meningeal enhancement	Inflamed leptomeninges with purulent meningeal exudate/infiltrate
Elevated protein (> 150 mg/dl –suspicion of TB meningitis, rarely seen in viral meningitis)	Hydrocephalus	Vasculitis, vascular necrosis and occlusion
Severely depressed glucose (<40 mg/dl)		

- **Repeated collection of CSF specimens for AFB culture and smear are necessary.**
  - In initial specimen, only 37% of cases detected positive AFB. Diagnostic yield increased to 87% when 4 specimens were tested.
  - For better yield, obtain large volume of CSF (10-15 ml)
- Epidemiologic information and travel history is very important.

- **Analysis of FFPE biopsy or autopsy tissue specimens using the combination of histopathology, PCR and IHC can be useful for:**

- *Diagnosis of unexplained death or unresolved case.*

  - Detection of unsuspected pathogens.

- *Identification and characterization of pathogens including Mycobacteria*

  - timely selection of specific antimicrobial therapy

  - directing appropriate public health responses

  - particularly helpful when appropriate specimens are unavailable or inadequate for conventional diagnosis.

- *Understanding the pathogenesis.*

Acknowledgements

Special Thanks:

Dr. Sherif Zaki
Chief, Infectious Diseases Pathology Branch, Division of High Consequence Pathogens and Pathology

Dr. Beverly Metchock
Team Lead, TB Reference Laboratory, Division of Tuberculosis Elimination

Dr. Christopher Paddock
Dr. Jeffrey Driscoll

Centers for Disease Control & Prevention, Atlanta, GA

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Specimen submission guideline can be found at:
http://www.cdc.gov/ncezid/dhcpp/idpb/specimen-submission/index.html