Clinico-Pathological Conference

Andrew W. Bollen DVM, MD
Professor of Pathology, UCSF

John Betjemann MD
Assistant Professor of Neurology, UCSF

Phil Larimer MD, PhD
Neurology Resident, UCSF

Disclosures

Betjemann- None
Bollen- None
Larimer- None

Case:

A 27 year old right-handed man presented with generalized convulsions.

Review of systems: Fatigue for two weeks

Allergies: None

Medications: None

Past medical history: None

Family history: None


Exam:

37.0, 103, 97/50, 19/min, 95% on RA
In no apparent distress
No meningismus, no lymphadenopathy
No cardiac murmurs, lungs clear bilaterally, abdomen soft

Neurologic Exam:

MS: Alert and oriented to self, place, date; speech fluent in Spanish, memory intact, follows commands briskly, left-sided visual neglect
CN: Pupils equal and reactive to light, no papilledema OU, extraocular movements are intact without nystagmus, trace left nasolabial fold flattening with symmetric activation, facial sensation intact bilaterally, tongue and uvula are midline, no dysarthria
Motor: No pronator drift, confrontational strength is without deficit
Reflexes: Biceps, triceps, and patellar reflexes are symmetric and 1+, plantar responses are flexor bilaterally
Sensation: Intact to vibration and temperature distally in all extremities
Coordination: Normal finger-nose-finger bilaterally
Initial Labs

CRP 5.2

14.8 > 12.7 / 247
36.9

5 cm CT head

5 cm FLAIR

5 cm T1 with gadolinium
Labs (normal unless otherwise noted):

- CRP 5.2
- CEA
- AFP
- CA 19-9
- CA 125
- Beta HCG
- TTE: Normal
- Computed tomography scans of the chest, abdomen, and pelvis as well as an ultrasound of the testicles did not reveal a primary neoplasm.
- CTA head/neck: normal
- CRP 5.2
- Serum cryptococcal antigen
- Serum cocci immunodiffusion and complement fixation
- HIV antibody and viral load
- CD4 228
- EBV PCR
- Cysticercosis IgG
- Toxoplasmosis IgG, IgM, PCR
- CSF (HD#4): 5 WBC (98% lymphocytes), 0 RBC, glc 83, protein 30, LDH 14, CrAg, cocci complement fixation, india ink, AFB smear, cysticercosis IgG
- Blood/CSF bacterial/AFB/fungal cultures: no growth

Therapies:

- Dexamethasone
- Albendazole
- Vancomycin, Ceftriaxone
- Metronidazole
- Cefazolin
- Imipenem/cilastin
- TMP-SMX
- Voriconazole
- Ambisome

Hospital Day

1 7 14 21 26 (transfer)
Clinical Course

Seizure LP → Mild encephalopathy and ongoing headaches → Brain Biopsy → Fever → Vancomycin, Ceftriaxone → Cefazolin → Cefipime → Metronidazole → TMP-SMX → Albendazole → Voriconazole/Vancomycin → Dexamethasone → Opiates for headache

1 7 14 21 26 (transfer) Hospital Day

Scan at day 26

FLAIR
T1 with GAD

FLAIR
T1 with GAD
He remained in coma with EEG demonstrating only diffuse slowing. Due to evidence of herniation on arrival, he was intubated and an EVD was placed. He had elevated intracranial pressure refractory to CSF diversion and medical management so had a decompressive hemicraniectomy on UCSF HD#3. He did not regain brainstem reflexes, was transitioned to comfort measures, and succumbed to his illness 35 days after initial presentation.
Approach and Overview

- Key points
  - History
  - Exam
  - Evaluation
  - Treatment
- Broad Differential Diagnosis (DDx)
- Further work up
- Diagnostic and treatment pearls
- Make a diagnosis

History and Exam- Key Points

- Young healthy man from Mexico working in agriculture
- Subacute onset of fatigue, encephalopathy, headache and new seizure
- Exposure to stray cats
- Exam: left visual neglect, facial asymmetry

Evaluation and Treatment- Key Points

- Labs
  - LP: not consistent with meningitis but was performed after 4 days of steroids and Abx
  - CD4= 228
- Imaging:
  - Initially multiple ring enhancing lesions with edema. New lesions on repeat scan despite treatment
- Treatment
  - Steroids
  - Polymicrobial, fungal, neurocysticercosis (NCC)
Differential Diagnosis

- Malignancy
  - Lymphoma
  - Multifocal CNS neoplasm/metastases
  - Gliomatosis Cerebri
- Sarcoid
- Infarct/vasculitis

- Infection
  - Pyogenic abscess
  - Septic emboli
  - Toxoplasmosis
  - Fungi
  - TB
  - NCC

Malignancy - CNS Lymphoma

- Pros
  - Encephalopathy, focal deficits, and seizures
  - Immunodeficiency

- Cons
  - Age
  - Usually more steroid responsive
  - Imaging

Malignancy - Multifocal glioma/CNS metastases

- Pros
  - Headache, seizures
  - Imaging: ring enhancing masses, gray-white, with edema

- Cons
  - Encephalopathy
  - Age
  - Lack of discernible primary
  - Dramatic progression after 3 weeks
Malignancy - Gliomatosis Cerebri

- **Cons**
  - Age
  - Usually more extensive radiographic involvement

Infection - Pyogenic Abscess

- **Pros**
  - History and exam
  - Ring enhancing lesions
- **Cons (none of these exclude the possibility!)**
  - Lack of fever
  - Negative blood cultures
  - CSF classically with pleocytosis and elevated protein
- **Septic emboli**
  - Negative TTE and blood CX, lack of other embolic strokes and absence of hemosiderin on GRE

Infection - Toxoplasmosis

- **Pros**
  - Immunodeficiency
  - Imaging: multiple ring enhancing lesions with edema
- **Cons**
  - Not quite immunodeficient enough
  - Negative serologies
    - Majority are IgG positive
    - PCR: 83% sens, 95% spec in CSF of AIDS-infected patients (similar in serum) (Alfonso Y, et al. 2009 and Mesquita RT et al. 2010)

Infection - Fungi

- **Cryptococcus**
  - Usually immunocompromised
  - Typically meningoencephalitis rather than discrete mass-like lesions (cryptococcomas)
  - CSF:
    - elevated OP, pleocytosis (lymphocytic), low gluc, high prot.
    - India ink, culture and CrAg (sens 93-100 and spec 93-98) (Tanner DC et al. 1994)
- **Aspergillosis**
  - Usually disseminated infection but can be local spread
- **Coccidomycosis**
  - Typically a meningitis, but can have abscess formation
  - CSF with lymphocytic pleocytosis
Infection- TB

**Pros**
- Imaging fits well with tuberculomas
- Low CD4 may serve as risk for TB or may be result of active TB
- CSF often nonspecific in tuberculomas
- Not treated empirically for TB
- Negative AFB smear and culture are not terribly helpful

**Cons**
- Classically causes a meningitis +/- tuberculomas
- Not from a truly endemic area
- CT chest without malignancy, but evidence of remote TB?

Infection- Neurocysticercosis

**Pros**
- Commonly presents with seizures and focal findings
- From an endemic area

**Cons**
- Imaging not classic-not truly cystic, no calcification, and no scolex
- Serum Ab testing negative (up to 98% sensitive) (Del Brutto OH 2012)
- New lesions despite albendazole

Neurosarcoïd

**Can impact any portion of the CNS without systemic manifestations**

**Imaging:** can see enhancing parenchymal lesions but also often meningeal enhancement and cranial neuropathies

**Initial treatment involves steroids**

Vasculitis

**Many of the above conditions can be associated with a vasculitis**

** Might somewhat explain the interval progression on MRIs**
Further Diagnostic Considerations

- Dental exam: source of bacteremia and septic emboli
- Ophthalmologic exam: sarcoid, lymphoma
- PET scan: potential biopsy target
- Labs: Beta-D-glucan, galactomannan

Diagnostic and Treatment Pearls

- CSF
  - Timing:
    - when possible LP prior to steroids and Abx
    - For cytology, CSF should be analyzed within few hours
  - For TB and lymphoma key is volume, volume, volume!
    - Lymphoma: cytology sensitivity 2-32% (Scott BJ, 2013). Lower yield with small CF volume, processing delays and steroids
    - TB: AFB smear~60%, PCR 56% sensitivity (Thwaites GE 2013)
- Steroids
  - Alter imaging, decrease diagnostic yield (lymphoma)

Diagnosis

- Lymphoma
- Pyogenic abscess
- Tuberculosis
- Fungal abscess
- Neurocysticercosis
- Neurosarcoid
- gliomatosis
- Toxoplasmosis
- Metastatic/multifocal glioma
- +/- vasculitis
Tuberculosis

Tuberculoma/Tubercular abscess


References


Recent Advances in Neurology -2015
Case: Neuropathology

Andrew Bollen MD, DVM
Department of Anatomic Pathology
Neuropathology Division
University of California San Francisco
Clinical presentation of CNS TB

Accounts for 1% of TB cases worldwide.
Occurs during primary infection in children or late reactivation infection in (often immunocompromised) adults.

**Tuberculous meningitis**
- From rupture of a subependymal tubercle into the subarachnoid space.
- Complicated by vasculitis and hydrocephalus

Three phases
- Prodromal: 2-3 weeks of malaise, headache, low-grade fever
- Meningitic: Meningismus, vomiting, confusion, focal signs
- Paralytic: Coma and seizures

Death is usually within 5-8 weeks of symptom onset if untreated
CSF has a high protein and low glucose with mild pleocytosis

**Intracranial tuberculoma**
- Signs of systemic illness or meningeal inflammation are rare
- CSF unremarkable

**Tubular arachnoiditis**

Radiological findings in CNS TB

**Tuberculous meningitis**
- Hydrocephalus or infarcts from arteritis on CT head
- Meningeal enhancement (typically basal) or pachymeningitis on MRI

**Intracranial tuberculoma**
- T1 isointense with ring enhancement
- Surrounded by T2 hyperintense vasogenic edema
- Not diffusion restricted

**Tubular arachnoiditis**
- Matted lumbar nerve roots

Sensitivity of diagnostic tests in CNS TB

**Tuberculous meningitis**
- CSF acid fast bacilli (AFB) smear has sensitivity of 10-91% (dependent the method)
- CSF AFB culture has 11-83% sensitivity
- CSF enzyme-linked immuno assay (ELISA) has 52-92% sensitivity
- CSF antigen assays have 38-94% sensitivity
- CSF PCR assays have 18-100% sensitivity

**Intracranial tuberculoma**
- CSF studies are not sensitive
- MRI and pathological biopsy are most diagnostic

Must maintain a high clinical suspicion!