Difficult Diagnosis:

Recent Advances in Neurology 2013

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Relevant Disclosures: None

Case History

- 50 yo right-handed woman developed “tingling” in the hands and arms, followed 3 days later by “excruciating pain” radiating down arms/upper back

- Ascending numbness in the feet, constipation, urinary urgency and right leg weakness...

7 months prior, she happened to have undergone a C-spine MRI after a car accident...
Case History

- CSF with no oligoclonal bands, culture no growth, normal cytology and flow cytometry
- Brain MRI normal
- Started high dose oral dexamethasone by neurosurgery and underwent anterior cervical discectomy/fusion at C3-7
- Arm pain resolved immediately post-operatively; numbness and weakness persisted

Case History

- Tapered steroids off completely over the next 6 weeks.
- Symptoms and exam remained stable
- Repeat MRI showed slight worsening

Case History

- Labs that were negative or normal:
  - Anti-aquaporin-4 IgG (NMO antibody)
  - ANA
  - HTLV I/II
  - ACE
  - RPR
  - HIV
- Repeat CSF exam:
  - 7 WBC (93% lymphs, 7% monocytes); 1 RBC
  - Total protein 41 mg/dL
  - Glucose 56 mg/dL (serum was normal range)
  - IgG index 0.5
  - No oligoclonal bands
- Imaging:
  - Brain MRI again normal
  - CT Chest/Abdomen/Pelvis with and without contrast unremarkable
She is referred for another opinion...

- General examination normal

- Fine-finger movements and foot taps slightly slowed on the right. Mild spasticity in both legs. Mild pyramidal weakness right IP and HS (4/5).

- Reflexes 3+ in UE and LE, plantar response flexor.

- Light touch reduced about 50% in the left foot

- 25-foot timed walk 4.5 seconds unassisted

Audience Response Question #1

What do you recommend for this patient as the next step?

A. Do no harm, repeat C-spine MRI in 3 months (assuming clinically stable)
B. Referral to neurosurgery for spinal cord biopsy
C. Bone marrow biopsy
D. PET Scan
E. Start appropriate immunosuppressive therapy for seronegative NMO (spectrum disorder)
F. Start appropriate DMT for multiple sclerosis – she has an atypical but classically-described variant

FDG-PET

Sarcoidosis

- Inflammatory disorder of unclear etiology characterized by non-caseating granulomas on histopathology

- Commonly invoked in neurological differential diagnosis

Endobronchial ultrasound guided biopsy: Non-caseating granulomas consistent with sarcoidosis, no evidence of infection or malignancy

PFTs: normal

Stage 1 Sarcoidosis

Non-caseating granuloma of sarcoidosis
**Epidemiology**

- Sarcoidosis is most common in Northern European and African-American populations

- Neurosarcoidosis ~1/100,000 person-years annual incidence in the U.K

- Peak age at onset in 30s-40s (working age)

**Practical Framework for CNS Sarcoidosis Diagnosis**

**Definite CNS Sarcoidosis** – CNS Biopsy, typical clinical syndrome & exclusion of other causes

**Probable Neurosarcoidosis** – Extra-CNS biopsy, typical clinical syndrome & exclusion of other causes

**Possible Neurosarcoidosis** – No pathology, typical clinical syndrome

There are many “steroid responsive,” “atypical” CNS inflammatory syndromes that are not necessarily “sarcoidosis”

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**UCSF CNS Sarcoidosis Experience**

<table>
<thead>
<tr>
<th>Total CNS Sarcoidosis</th>
<th>Definite Cases (CNS Biopsy)</th>
<th>Probable Cases (Extra-CNS Biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=41</td>
<td>n=19 n=22</td>
</tr>
<tr>
<td>Age at neurological syndrome onset</td>
<td>40 years (IQR 35 to 49), range 21-66 years</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Known sarcoidosis at neuro syndrome onset</td>
<td>5 (12%)</td>
<td></td>
</tr>
<tr>
<td>Evidence of pulmonary sarcoidosis at time of neurological presentation</td>
<td>24 (62%)</td>
<td></td>
</tr>
<tr>
<td>Evidence of any extra-CNS sarcoidosis at time of neurological presentation</td>
<td>72% (28% truly had “isolated” neurosarcoidosis)</td>
<td></td>
</tr>
<tr>
<td>Whole Body PET provided diagnostic insight beyond conventional CT</td>
<td>4/8 (50%)</td>
<td></td>
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</tbody>
</table>

**UCSF CNS Sarcoidosis Experience**

<table>
<thead>
<tr>
<th>Biopsy Proven CNS Sarcoidosis n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ACE Elevated (&gt;67)</td>
</tr>
<tr>
<td>CSF ACE elevated</td>
</tr>
<tr>
<td>CSF Pleocytosis (&gt;5 WBC)</td>
</tr>
<tr>
<td>CSF Protein elevation (&gt;50)</td>
</tr>
<tr>
<td>CSF Glucose Abnormally Low</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
</tr>
<tr>
<td>Present (2 or more)</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>N=26</td>
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<td></td>
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</tbody>
</table>

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Gelfand, et. al, manuscript in preparation
Practical Approach to Diagnosis of CNS Sarcoidosis...

- A chest CT with contrast is probably the most helpful test to survey for pulmonary involvement.
- When the chest CT is negative, a whole-body FDG-PET can be invaluable to identify sites of metabolically active disease, including “hot” but normal size lymph nodes (50% hit rate in our series).
- Image the entire neuroaxis for biopsy targets.
- A tissue diagnosis is favored when the risk is acceptable.
- ACE not that helpful for CNS disease.

CNS Sarcoidosis – MRI Observations

1) Tends to seed within the CNS at favored neuroanatomic sites and can persist for months to years at a time with ongoing enhancement.

1) Nodular/lobulated enhancement on MRI is a sign of active disease; often involves nearby meninges.

2) “Relapses” tend to occur at sites of previous activity (Beware of new symptoms completely out of the blue!)

Nodular enhancing appearance on MRI

Syndrome: Optic Neuropathy

CNS Biopsy: Noncaseating Granulomatous Inflammation

Nodular enhancing appearance on MRI

Syndrome: Hypopituitarism

Sagittal T1 Post-Gad over time shows extension into periventricular meningeal spaces.
**Nodular, infiltrative, lobulated contrast-enhancement Syndrome: Myelopathy**

- T2 Sagittal
- T2 Axial
- T2 Post-Gad
- T1 Post-Gad

**A Decade of Brain Biopsy-Proven CNS Sarcoidosis:**
The disease extends and spreads through regional propagation

- Corticosteroids + Azathioprine
- Hypopituitarism
- Blindness
- Cognitive Impairment

**Our usual approach to disease modifying therapy for CNS Sarcoidosis**

1) First-line therapy with glucocorticoids (start high and taper cautiously)

2) Second-line therapy with weekly oral methotrexate (up to 20 mg/week), azathioprine or mycophenolate

3) Infliximab (TNF-alpha inhibitor)
**TNF-alpha inhibition in sarcoidosis**

- 2 RCTs of infliximab in pulmonary sarcoid – modest benefit in lung function
- 1 RCT of infliximab in “extrapulmonary sarcoid” – reduced a composite disease severity score
- Small case series in CNS sarcoidosis report benefit
- Not all TNF-alpha inhibitors are the same – some make sarcoidosis worse!

**TNF-Alpha Inhibition is associated with demyelinating disease**

- Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2

**TNF neutralization in MS**

Results of a randomized, placebo-controlled multicenter study

Lenercept made MS worse compared to placebo

**Dramatic Improvement within weeks of starting Infliximab after 6 years of unrelenting disease**

- After treatment with infliximab

**Audience Response Question #2**

What major neurological adverse effect is associated with TNF-alpha inhibitors?

1. Small fiber neuropathy
2. Demyelinating disease
3. Meningioma
4. Stroke
5. Reduction of seizure threshold
Case resolution – Our patient from today

Baseline 3 months 6 months 8 months

Start Infliximab + MTX

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