**Key Features**

- **Rapidly progressive dementia**
  - onset with fatigue and rapid decline over 3-4 months
- **Focal neurological deficits**
  - left visual field deficit; left hemiparesis
- **Abnormal Brain MRI**
  - progressive disease involving sub-cortical white matter
  - Abnormal chest imaging and lung biopsy
  - No response to corticosteroids

**Rapidly Progressive Dementia**

- **Prion Diseases** – 62%
  - Sporadic CJD – (46%)
  - Genetic – (13.6%)
  - Acquired CJD – (1.7%)
- **Neurodegenerative Diseases** – 39%
  - Corticobasal ganglia degeneration
  - Fronto-temporal dementia
  - Dementia with Lewy bodies
  - Alzheimer Disease
  - Progressive supranuclear palsy
- **Autoimmune Disorders** – 22%
- **Unknown** – 12%
- **Infectious** – 6%
- **Malignancy** – 6%
- **Toxic-Metabolic** – 4%
- **Vascular** – 3%

**Rapidly Progressive Dementias**

- UCSF evaluation of 178 cases of suspected prion disease 2001-2007
- Conclusive diagnosis in 95.5%
- 4.5% - dementia, leukencephalopathy, or encephalopathy of unknown origin.

![Brain MRI – 06/17 DWI (-) and Contrast enhance (-)]

![Brain MRI – 06/17 DWI (-) and Contrast enhance (-)]

**CPC**

Winston Chiong MD, PhD
Gary M. Abrams MD
Andrew Bollen DVM, MD

![Graph](Graph.png)
**Prion Disease – Sporadic CJD**

- Dementia with cerebellar, pyramidal, extrapyramidal, and behavioral/psychiatric symptoms
- Median age of 68; Males = Females
- Median survival – 5 months; 85% mortality – 1 year
- Non-specific onset in 30-35% - fatigue, headache, sleep disturbance, vertigo, malaise, weight loss, pain, depression, or behavioral changes - weeks to months prior to dementia

**Prion Disease - UCSF**

Combination of FLAIR and DWI MRI had 91% sensitivity and 94% specificity – most sensitive diagnostic test
- 66% of patients had DWI or FLAIR abnormalities in cortex and deep gray matter (striatum or thalamus) – (A)
- 25% had cortical changes only – (B)
- 5% had isolated changes in deep gray matter structures – (C)
- White matter abnormalities are rare

**Rapidly Progressive Dementia**

- Neurodegenerative Diseases
  - Corticobasal ganglia degeneration
  - Frontotemporal dementia
  - Dementia with Lewy bodies
  - Alzheimer disease
  - Progressive supranuclear palsy
- Autoimmune Disorders
- Infectious
- Malignancy
- Toxic-Metabolic
- Vascular

**Neurodegenerative Diseases**

- Corticobasal ganglia degeneration (8)
- Frontotemporal dementia (7)
- Dementia with Lewy bodies (4)
- Alzheimer disease (5)
- Progressive supranuclear palsy (2)

- Extrapyramidal signs (e.g. parkinsonism) or myoclonus are common – can be confused with CJD
- Our case - Progressive white matter disease on imaging not consistent
**Toxic-Metabolic**

- Many causes – (electrolytes, calcium, magnesium, phosphorus, vitamin B12, renal and liver function)
- Porphyria
- Bismuth intoxication
- Vitamin deficiencies
- Heavy metal intoxications – As, Pb, Hg, Al
- **Our case** –
  - No abnormal laboratory chemistries
  - Presence of focal neurological deficits
  - Abnormal head CT and brain MRI

**Rapidly Progressive Dementia**

- **Autoimmune**
  - Hashimoto
  - Multiple sclerosis
  - Paraneoplastic
  - Celiac disease
  - Sarcoidosis
- **Infectious**
- **Malignancy**
  - CNS lymphoma
- **Vascular**
  - Vasculitis

**Key Clinical Features**

- **Rapidly progressive dementia** – onset with fatigue and rapid decline over 3-4 months
- **Focal neurological deficits** – left visual field deficit; left hemiparesis
- **Abnormal Brain MRI** – progressive disease involving sub-cortical white matter
- **No response to corticosteroids**
- **Abnormal chest imaging and lung biopsy**

**Hashimoto Encephalopathy**

- **Unknown etiology** – associated with Hashimoto thyroiditis; probably immunological origin
- **75% of cases occur in women**
- **Variable neurological signs** – altered consciousness, seizures, extrapyramidal signs, ataxia, or stroke.
- **Psychiatric features are frequent**
- **Increased levels of anti-thyroid antibodies (anti-thyroperoxidase and anti-thyroglobulin)**
- **Thyroid function is variable**
- **Almost always responsive to corticosteroids**

**Brain MRI – 06/17; DWI (-); Enhancement (-)**

**Brain MRI – 07/07**
**Paraneoplastic**
- Dementia associated with anti-neuronal antibodies
- Clinical picture - limbic encephalopathy
- 2/3 of patients have multifocal nervous system disease
- Diagnosis is by antibody detection in serum or CSF – antibody is not always identified

**Celiac Disease**
- Gluten sensitivity - typically causes GI symptoms
- Dementia, ataxia, and neuropathy even in the absence of gastrointestinal symptoms
- Lab – anti-gliadin antibodies (gliadin is component of wheat)
- Etiology of neurological symptoms unclear
  - Immune-related
  - Vitamin deficiencies
- Treatment – some patients may respond to gluten free diet.

**Paraneoplastic**
- Anti-Hu and anti-CV2 antibodies – most common
  - Small-cell lung cancer; tumor treatment may help
- Anti-Ma2
  - Testicular cancer; responsive to tumor or immunologic treatment
- Anti-N-methyl-D-aspartate receptor
  - Ovarian teratomas; no tumor found in 40% of cases
- Anti-voltage gated potassium channels (VGKC)
  - May be seen in non-neoplastic disorders.

**Celiac Disease**

CNS Lymphoma

- Sub-acute dementia usually in setting of immunosuppression
- Typically non-Hodgkins B-cell type
- Diagnosis:
  - CSF:
    - Increased protein
    - Increased glucose
    - Lymphocytosis
    - Cytology may not be helpful
  - Biopsy often required
  - 70% respond to corticosteroids

Brain MRI

- Iso-intense/mildly hyperintense T2-weighted signal
  - Basal ganglia
  - Periventricular white matter
  - Corpus callosum
- 50-70% are solitary lesions- but may be multiple
- +/- contrast enhancement; DWI often abnormal
- Frequently have some edema

Rapidly Progressive Dementia

- Autoimmune
  - Multiple sclerosis
  - Sarcoïdosis
- Infectious
- Vascular
  - Vasculitis
- Age
- Unusual presentation
- Lack of supporting laboratory findings
- Atypical imaging

Age < 45

- Review of cases at Mayo Clinic from 1996-2006
- Ages 17-45
- Identified 22 cases
- Severe dementia to death over 18 months
- Creutzfeldt-Jakob disease*
- Fronto-temporal dementia
- Paraneoplastic limbic encephalitis
- Microvascular ischemic disease
- Neuronal ceroid lipofuscinosis
- Adult-onset leukodystrophy
- Fahr disease
- MELAS
- PML

* Kelley et al. Cog Behav Neurol. 2009
Key Features

- Rapidly progressive dementia – onset with fatigue and rapid decline over 3-4 months
- Focal neurological deficits – left visual field deficit; left hemiparesis
- Abnormal brain imaging with progressive disease involving sub-cortical white matter
- No response to corticosteroids
- Abnormal chest imaging and lung biopsy

Our Case – Chest Imaging

Interstitial and nodular pattern
Bilateral perihilar airspace opacities

Stage 1 - Sarcoidosis
Stage 3 - Sarcoidosis

Our Case – Lung Biopsy

Compact granulomas; macrophages
No evidence of necrosis

Differential
Fungi – special stains (-)
TB – special stains (-)
Berylliosis – no exposure
Sarcoid

Extensive reticulonodular lesions concerning for sarcoid or lymphoma
Normal axial chest
Sarcoidosis

- Neurologic complications occur in 5 - 15%
- Pathogenesis – compact granulomas; environmental exposure in genetically susceptible individuals
- Common neurological syndromes:
  - Cranial neuropathies – 50-75% ; Cranial nerve VII most common
  - Focal neurological deficits
  - Granulomatous perivascular inflammation can cause seizures, vasculopathy, or encephalopathy
  - Hypothalamic-pituitary dysfunction
  - Myelopathy or radiculopathy
  - Meningitis

Terushkin et al. The Neurologist - January 2010

Sarcoidosis

Neuro-diagnostic Tests

- CSF exam – 1/3 are normal
  - Protein increased in 66%
  - Glucose – low or normal
  - Mononuclear pleocytosis – 50%
  - IgG index may be elevated; oligoclonal bands may be present
  - CSF ACE may be elevated – not reliable norms; increased in carcinomatous and infectious disease
- There are no uniformly helpful neuro-diagnostic tests

Terushkin et al. The Neurologist January 2010

Brain MRI in Sarcoid

- Normal
- Enhancing granulomas
- Enhancing or non-enhancing, T2-weighted, white matter hyperintensities
- Thickening of basilar leptomeninges (typical of chronic meningitis)
- DWI hyperintensities resembling Creutzfeldt- Jakob

Terushkin et al. The Neurologist - January 2010

White and gray matter lesions in neurosarcoid

Pawate, S. et al. QJM 2009 102:449-460

2/13/2010
Enhancing parenchymal sarcoid nodules

Meningeal enhancement

Mass lesion - Apparent glioma

Extra-axial mass

Pawate, S. et al. QJM 2009 102:449-460
Sarcoid vasculitis

Sarcoidosis

- Treatment –
  - If feasible, biopsy should be done prior to empiric treatment
  - First line is corticosteroids - 40-80 mg prednisone/day with taper based on symptom response
  - Multiple other immunomodulatory agents have been used to successfully treat neurosarcoid

<table>
<thead>
<tr>
<th>Severe symptoms</th>
<th>Mild/moderate symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV infliximab (aTNFα)</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
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<tr>
<td></td>
<td>Azathioprine</td>
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<tr>
<td></td>
<td>Hydroxychloroquine</td>
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</tbody>
</table>

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Neurosarcoidosis

- If neurosarcoid is the clinical presentation - <25% may have systemic signs
  - Uveitis
  - Rash
  - Respiratory symptoms
- Diagnostic work-up:
  - Ophthalmologic exam
  - CXR – may be positive in 25-65%
  - Serum ACE level – may be helpful if elevated, but non-specific
  - Imaging MR, FDG-PET, etc for biopsy

Rapidly Progressive Dementia

- Infectious
- Vascular
  - Vasculitis
### Vascular
- Primary CNS vasculitis or granulomatous angiitis
- Vasculitis with systemic disease:
  - Polyarteritis nodosa
  - Sarcoidosis
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Bechet disease
  - Hypereosinophilic syndrome
- Dx – Systemic signs; laboratory; imaging

### Infectious
- Herpes simplex viruses 1 and 2
- Cytomegalovirus,
- Epstein–Barr virus,
- West Nile virus
- Enterovirus
- Polymeroviruses - JC and BK viruses
- Human immunodeficiency virus
- Mycoplasma pneumoniae and neoaerum
- Bartonella henselae (cat scratch disease)
- Whipple disease (Tropheryma whippeli)
- Cryptococcus neoformans
- Trypanosomiasis
- Malaria

### A diagnostic procedure was performed...
- **Brain Biopsy**
  - Chest pathology with positive biopsy
  - Compatible neurological syndrome
  - Compatible Brain MRI
  - Previously seen at UCSF as a diagnosis of rapidly progressive dementia

### The Association of Progressive Multifocal Leukoencephalopathy and Sarcoidosis
Mark A Rosenbloom, M.D.; and Dean F. Upoff M.D.
*Chest* 1983;83:572-575

“A 59-year-old woman had a right homonymous hemianopsia, memory impairment for five months, a non-enhancing area in the left parieto-occipital region on CT scan, and bilateral reticulonodular infiltrates on chest x-ray film. Lung biopsy findings were consistent with sarcoidosis, a clinical diagnosis of CNS sarcoidosis made, and prednisone therapy begun. She deteriorated neurologically and died. At autopsy characteristic histologic and electron microscopic features of progressive multifocal leukoencephalopathy (PML) were found. We conclude that this and other cases demonstrate an association of PML and sarcoidosis and that steroid treatment is not a precondition. ……”

### Progressive Multifocal Leukoencephalopathy
- CNS demyelination associated with reactivation of the polyoma JC virus
- Primary infection with JCV occurs in childhood: antibodies can be found in 86% of adults
- PML is opportunistic infection associated with:
  - HIV infection/AIDS
  - Hematologic and solid organ malignancies,
  - Organ transplant recipients
  - Granulomatous and inflammatory diseases
Progressive Multifocal Leukoencephalopathy

- PML usually manifests with sub-acute neurologic deficits including:
  - Altered mental status
  - Motor deficits (hemiparesis or monoparesis),
  - Limb ataxia or gait ataxia
  - Visual symptoms such as hemianopia and diplopia.
- Average survival is 2.6 mos. in patients without HIV
- Sarcoidosis - ~10 well-documented cases in literature

Progressive Multifocal Leukoencephalopathy

- Brain biopsy is gold standard for diagnosis
- Treatment not successful:
  - Cytarabine – interferon alpha 2b – cidofovir – topotecan mirtazapine
  - In HIV patients – HAART should be optimized
  - Stop immunocompromising drugs
  - High dose glucocorticoid for inflammation

Summary

- 58 y.o. man with:
  - Rapidly progressive dementia and focal neurological deficits
  - Brain MRI showing progressive subcortical white matter disease
  - Reticulonodular lung disease with biopsy c/w sarcoidosis
  - A downhill course that was unresponsive to corticosteroid treatment
- He underwent a brain biopsy
- Findings should have been neurosarcoidosis
- The final diagnosis: Progressive multifocal leukoencephalopathy
### Vascular

- Rare cause of rapidly progressive dementia
- Strokes including large vessel occlusions, thalamic or multifocal infarcts, thrombotic thrombocytopenic purpura
- Diminished cerebral perfusion - hyperviscosity syndromes with polycythemia or monoclonal gammopathies
- Venous thrombosis and dural arterio-venous fistulas
- Neuroimaging distinguishes these conditions