

A white horse is grazing in a green field. In the background, there are trees with bright yellow autumn leaves. A dark wooden fence runs across the middle of the image. The sky is overcast.

Diagnosing PML

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For Session 4: Ongoing Research
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Standard PML Diagnostic Measures

- Clinical Diagnosis
 1. Clinical manifestations c/w PML
 - Examples: Hemiparesis, sensory abnormalities, hemianopsia, aphasia, dysarthria, behavior changes
 - Exclude such findings as optic neuritis and myelitis

PML in AIDS - Clinical Features

(in descending order of frequency)

- **Symptoms**

- Weakness
- Cognitive impairment
- Speech abnormalities
- Headache
- Gait impairment
- Visual abnormalities
- Sensory loss
- Seizures
- Limb incoordination

- **Signs**

- Hemiparesis
- Gait disturbance
- Cognitive impairment
- Dysarthria
- Dysphasia
- Hemisensory loss
- Visual field defect
- Ocular palsy

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 2. MRI features c/w PML

Radiographic Characteristics of PML

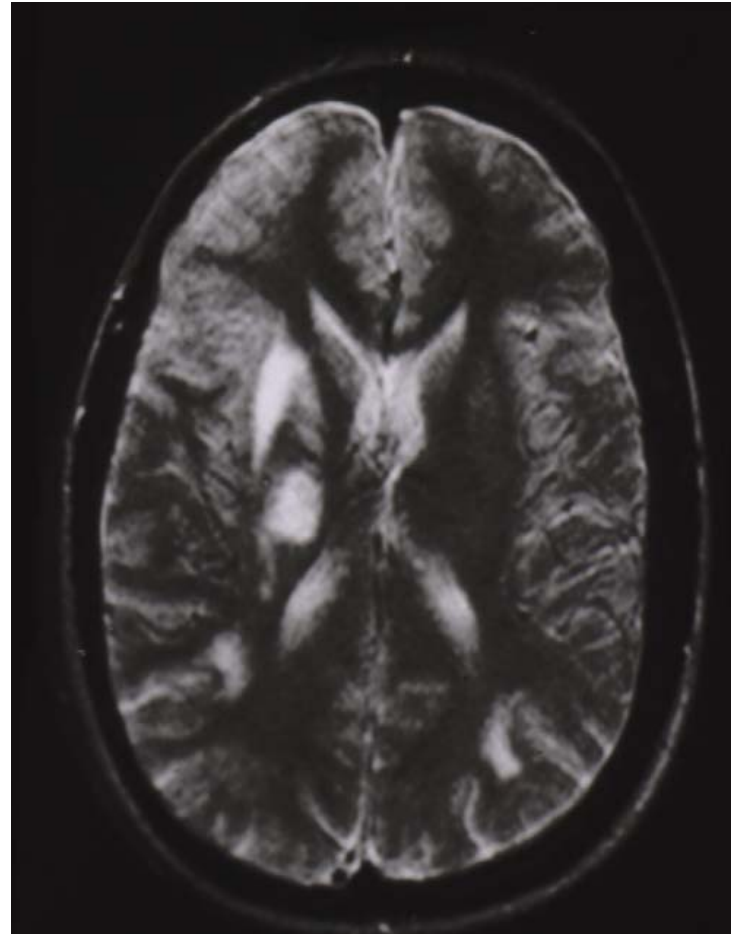
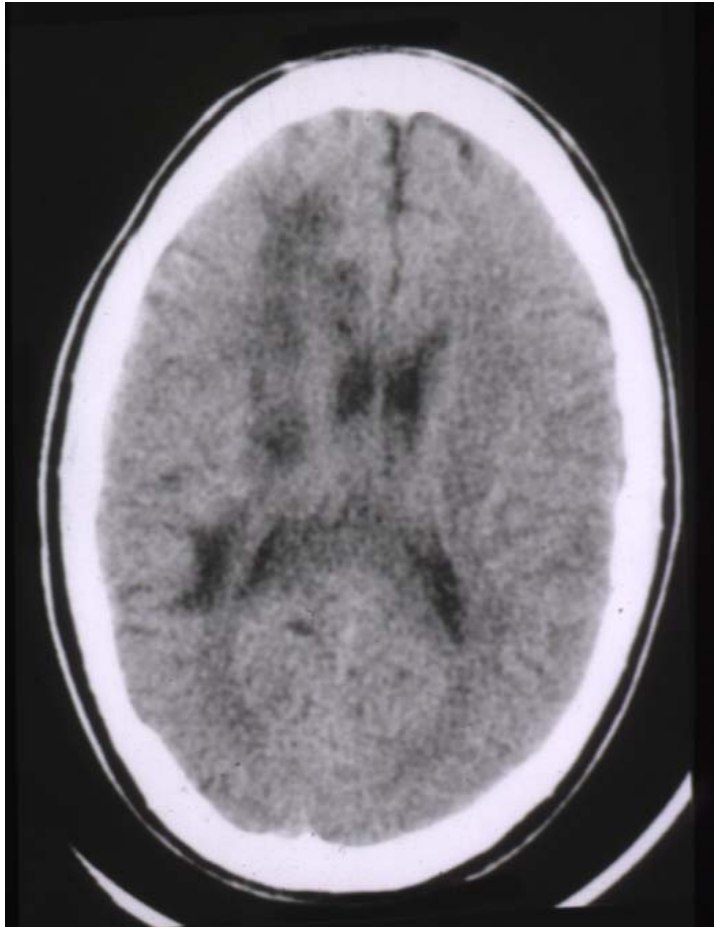
CT Scan

- hypodense lesions
- rare contrast enhancement

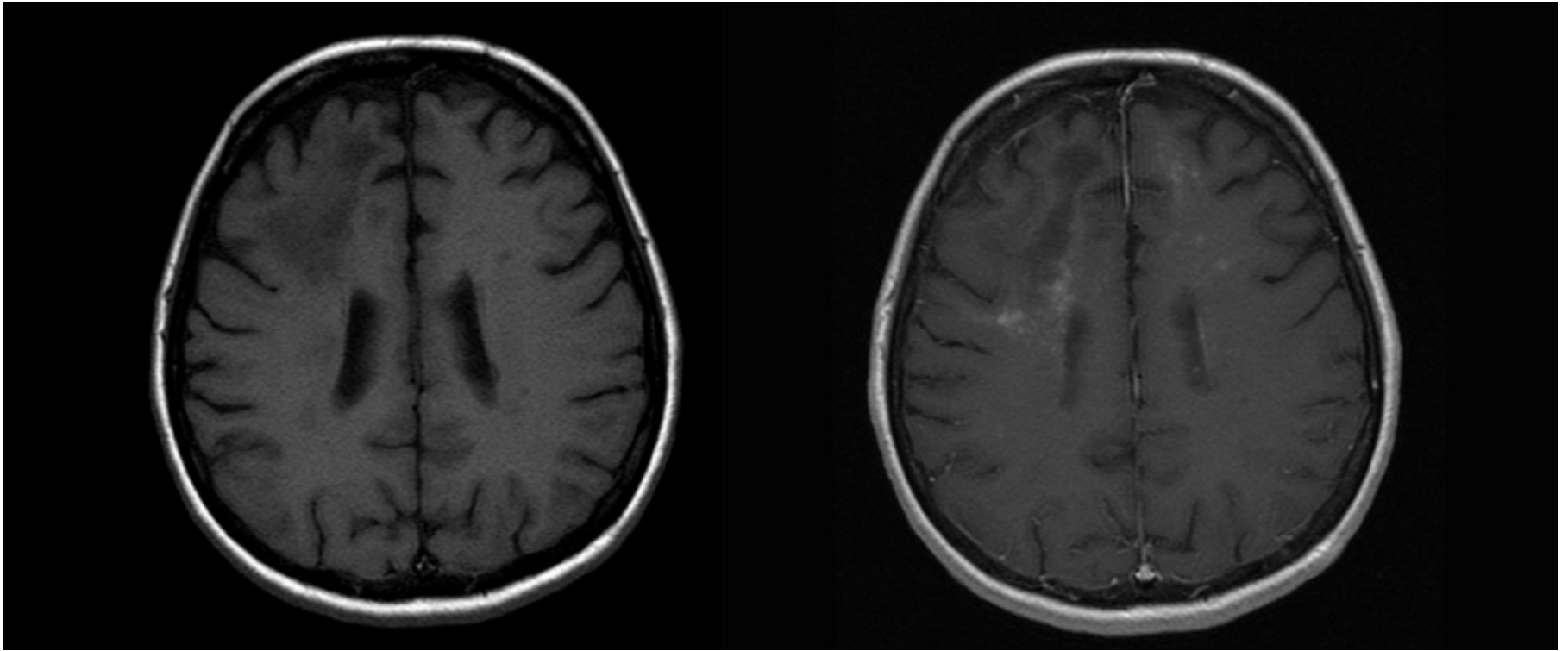
MRI

- increased signal on T2WI and FLAIR
- hypointense on T1WI
- no mass effect (present occasionally with IRIS)
- often parieto-occipital and frontal lobes
- atypical locations
 - cerebellum, brainstem, basal ganglia, temporal lobe
- Gd enhancement speckled or thin rim (30-40% of natalizumab associated PML; <15% of AIDS)

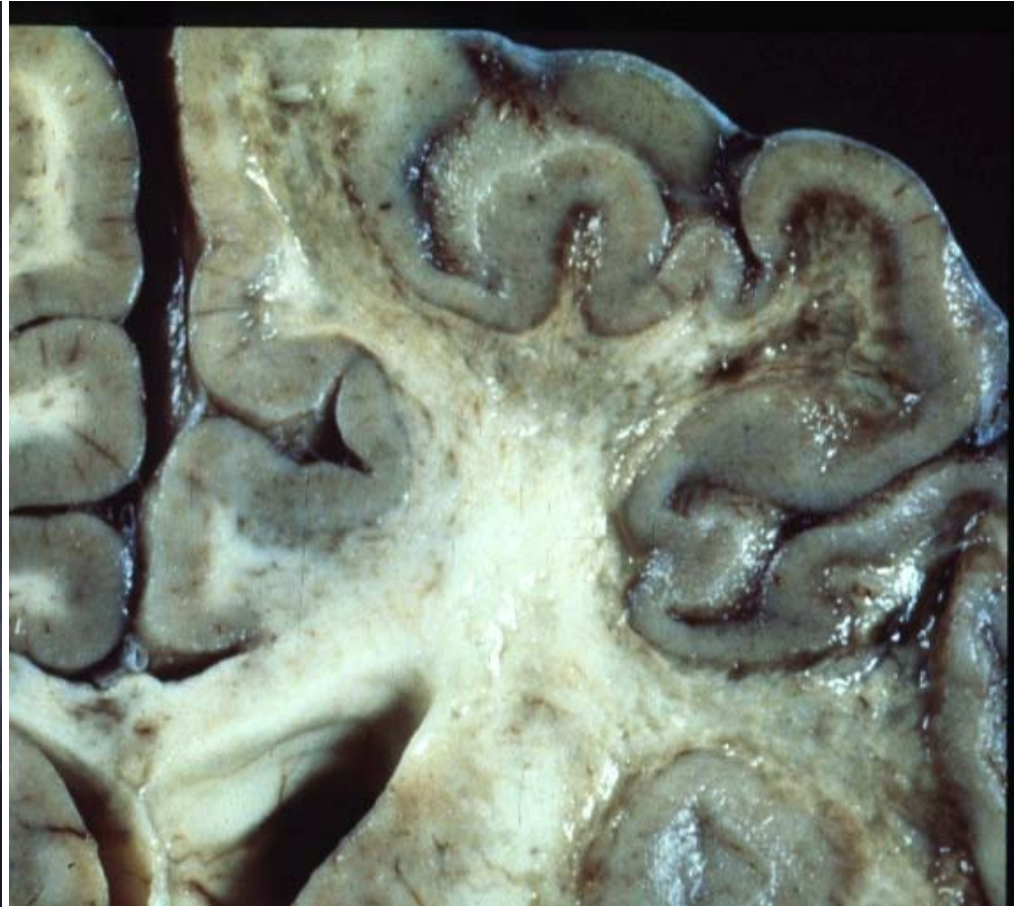
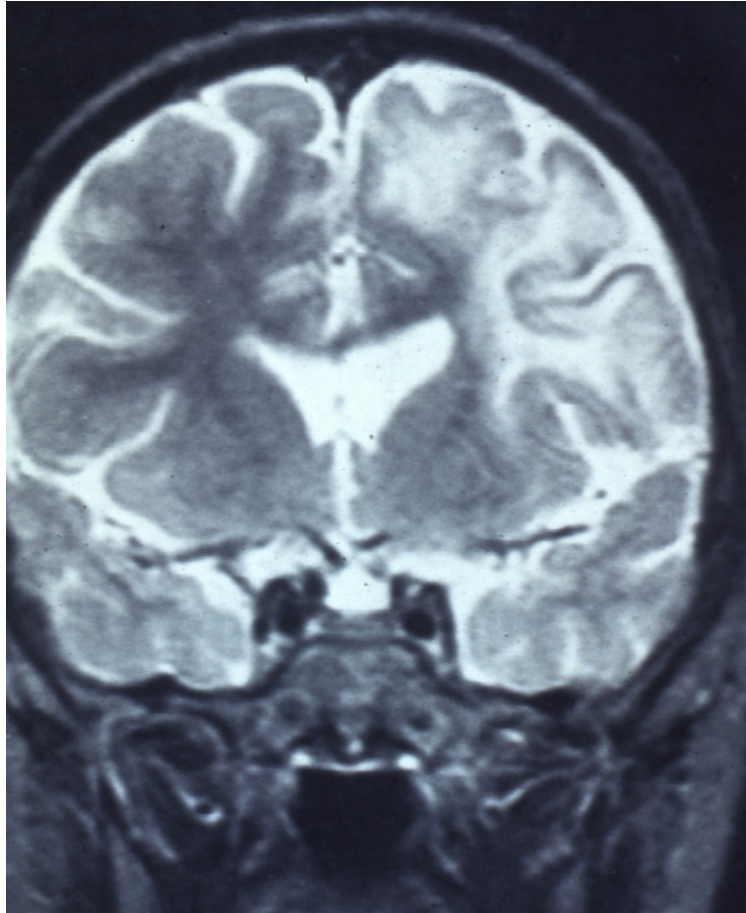
CT and MRI in PML



Contrast enhancement of MRI



Radiologic-Pathologic Correlation in PML



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 2. MRI features c/w PML
 3. CSF JCV+ by PCR

PML

CSF Caveats

- False negatives
 - Routine PCR – 25%
 - Ultrasensitive PCR – 5%
- False positives (?)¹
 - 2/217 (0.9%) MS CSF with JCV+
 - 1/210 (0.5%) cell free CSFs – 103 copies/ml
 - 1/42 (2.4%) CSF cell samples – 25 copies/ml
 - Low copy numbers
- Persistently positive CSF JCV PCR²
 - 13/35 MS patients with natalizumab PML CSF JCV+ after IRIS
 - Up to 5 months out JCV still detectable

Gold Standard for PML Diagnosis

- Brain pathology at biopsy or autopsy

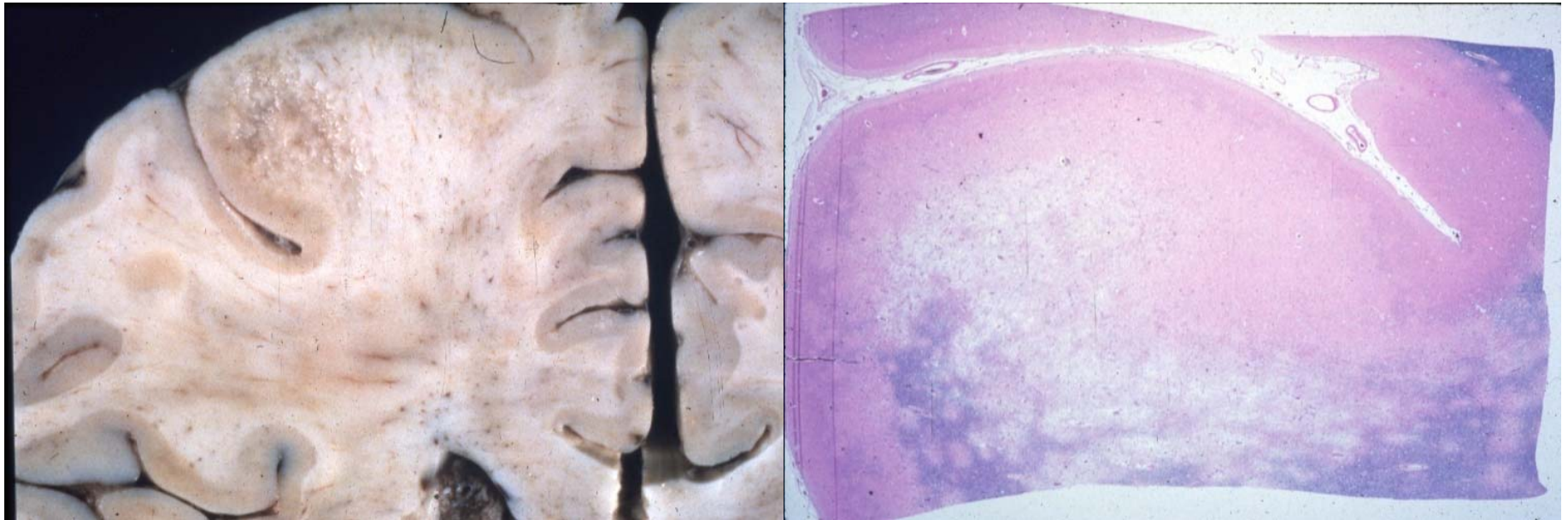
Characteristic histopathological triad

1. Demyelination
2. Bizarre astrocytes
3. Enlarged oligodendroglial nuclei

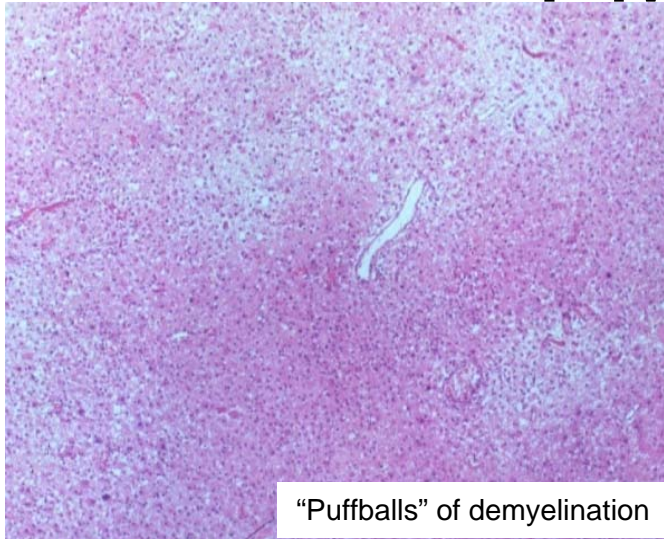
Demonstration of the virus by EM or
immunohistochemistry

PML

Demyelination in PML



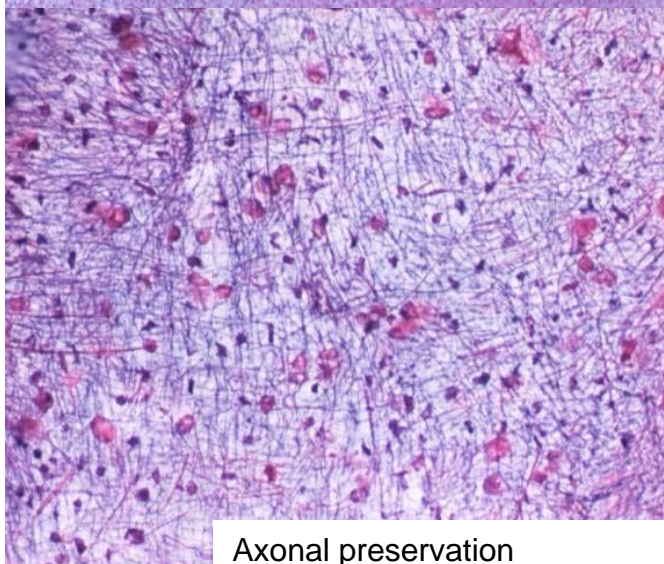
Classic Histopathological Triad of PML



"Puffballs" of demyelination



Bizarre astrocytes



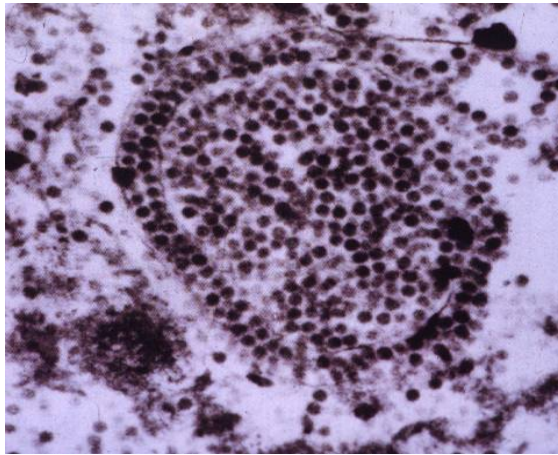
Axonal preservation



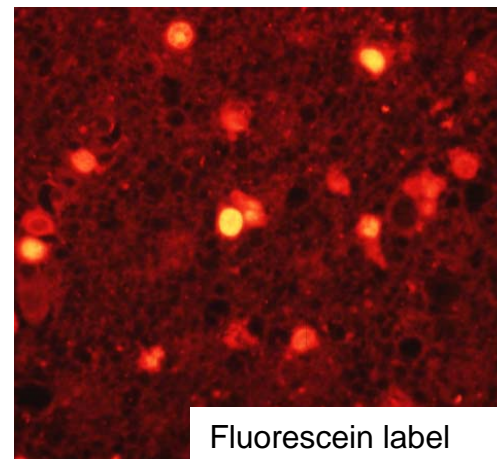
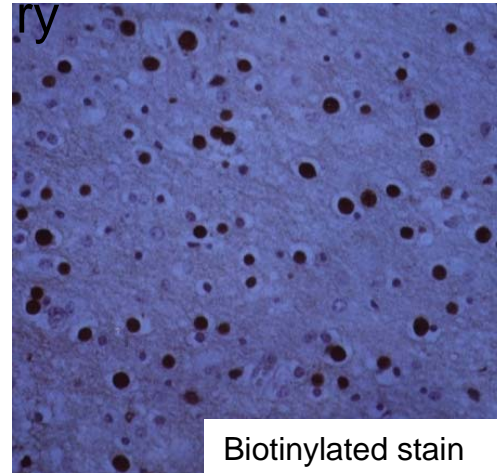
Enlarge oligodendroglial nuclei

Demonstration of JCV in Tissue

Electron microscopy

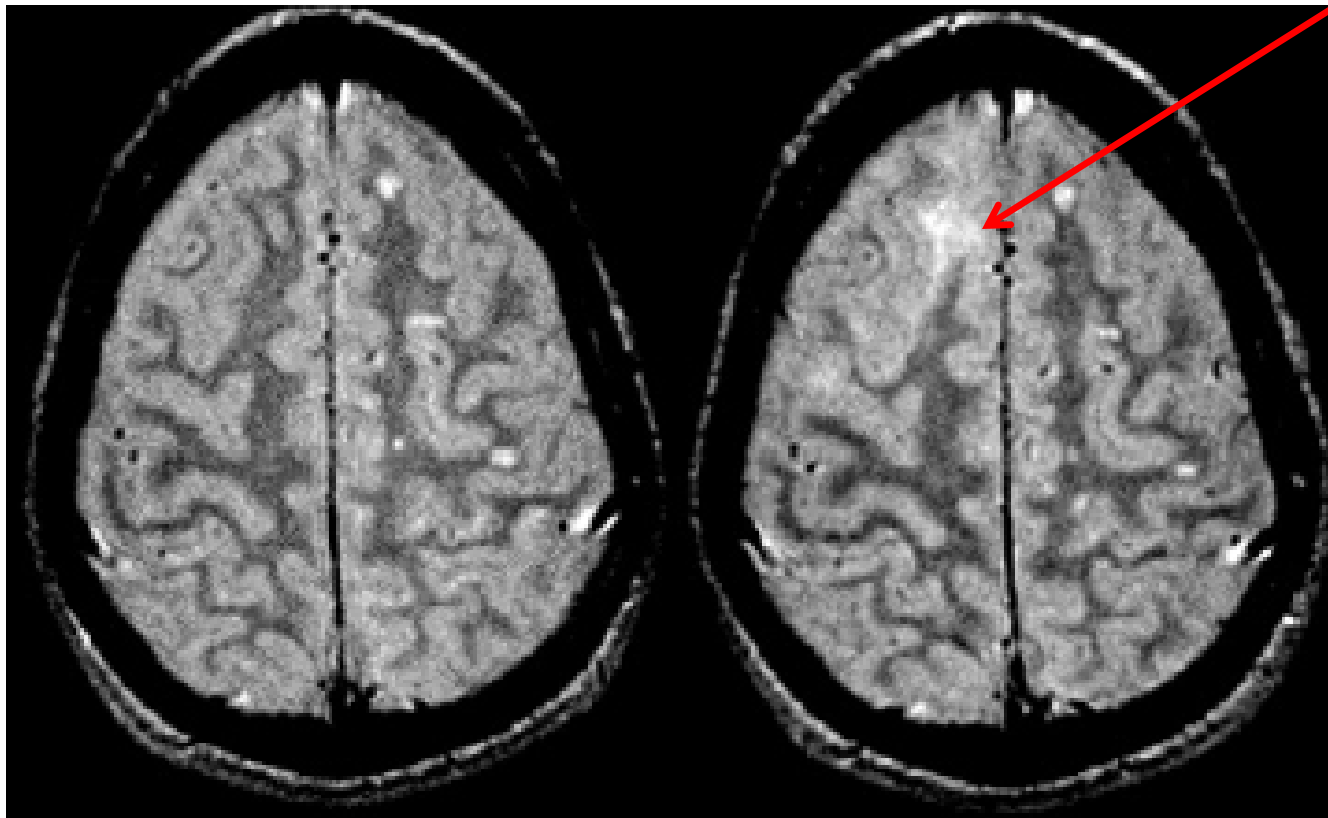


Immunohistochemistry



Radiographically Isolated PML

- 23 year old man with MS on natalizumab for 24 months shows new lesion. One month later he is recognized to have inappropriate behavior on routine visit.

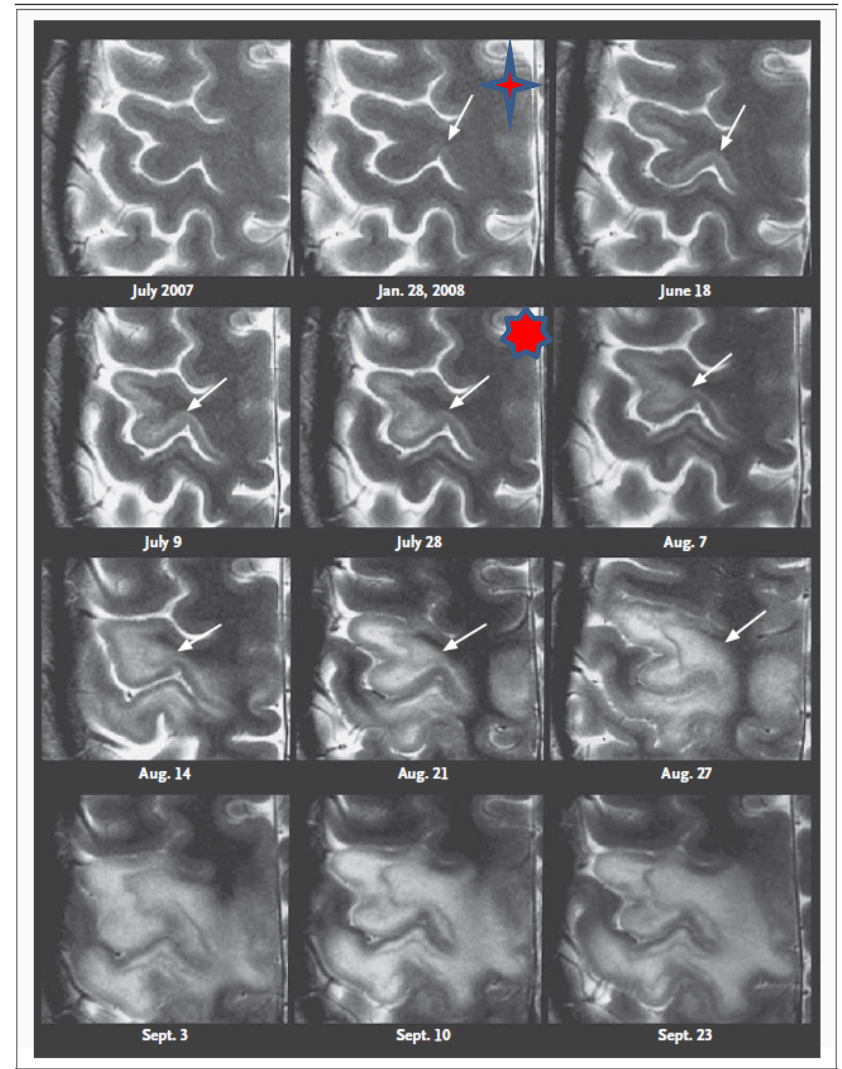


October 2003

October 2004

Radiographically Isolated PML

- 35 year old man started on natalizumab in Jan 2007
- Jan 2008 MRI shows early lesion (read as no new lesions)✦
- Developed myoclonic jerking of left arm in Apr 2008
- MRI abnormality evident by Jul 2008✦

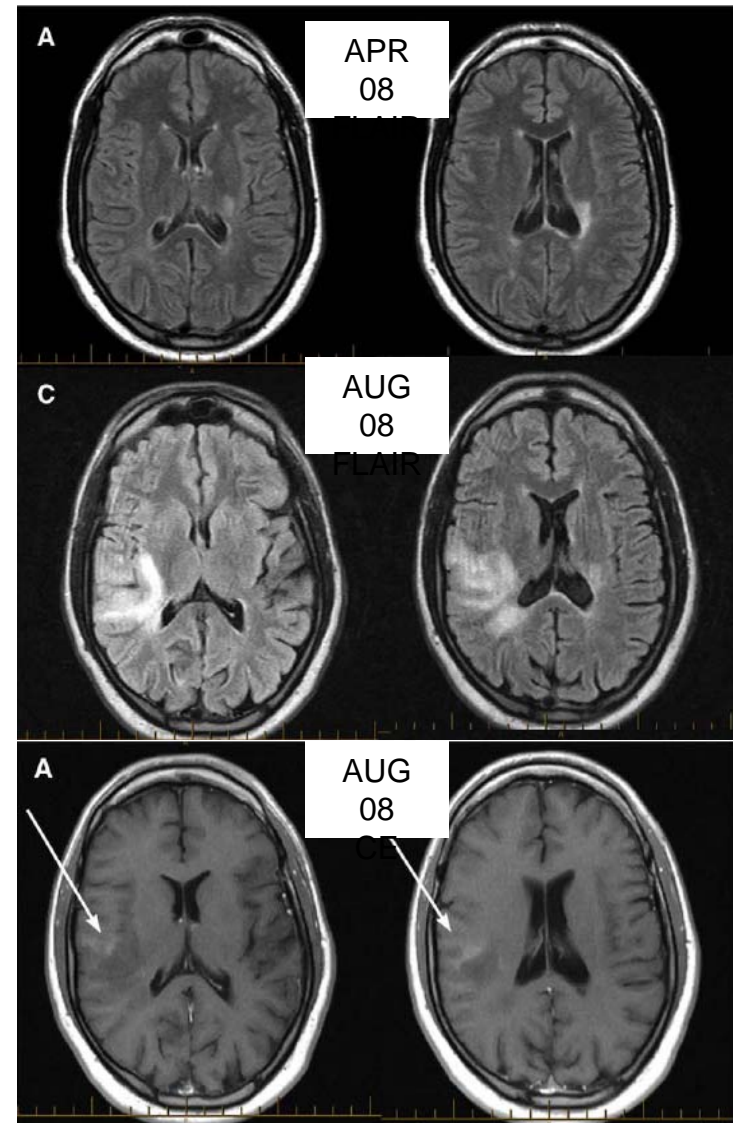


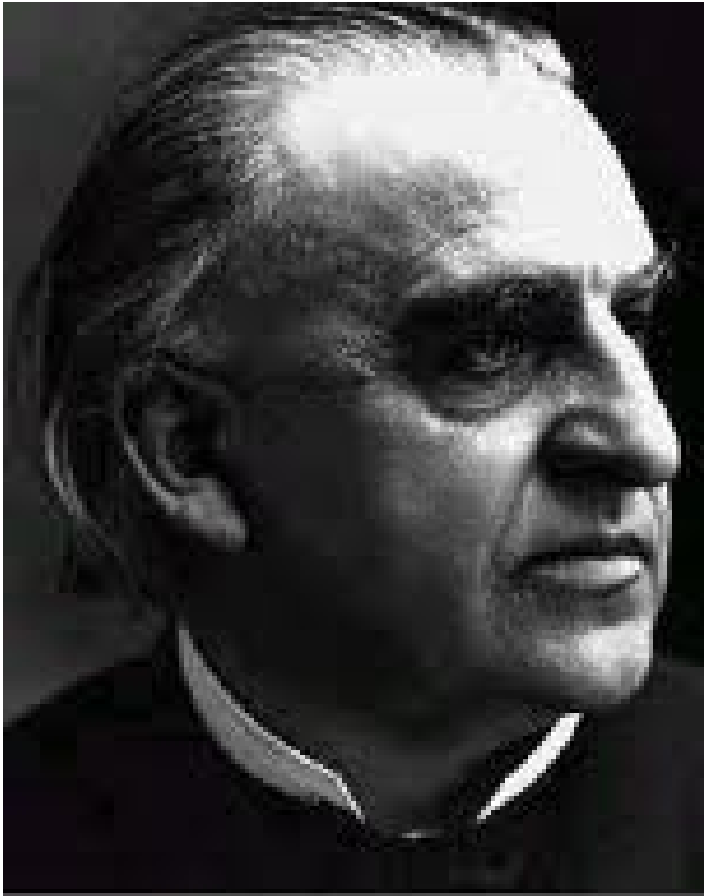
Radiographically Isolated PML

- A high index of suspicion of PML must be entertained even in the absence of any clinical manifestations
- Diagnostic criteria must be expanded to permit diagnosis of PML based on radiographic and laboratory criteria (CSF JCV PCR +)

PML Diagnostic Uncertainty

- 27 year old man with MS symptoms since teens
- MS dx established in 2006
- Apr 2008, natalizumab start
- Allergic reaction with infusions
- Aug 2008, 1 month after 4th infusion, presents with confusion, behavioral changes and worsening left hemianesthesia and dysarthria
- CSF: 14-28 WBCs; prot 55; IgG index 2.5; MBP 4.9; JCV PCR negative x 2
- 1 dose of IVMP and PLEX
- Significant recovery and alive at 36 months
- Giant MS plaque or aborted PML with negative CSF





To learn how to treat disease, one must learn how to recognize it. The diagnosis is the best trump in the scheme of treatment.

Jean Martin Charcot
1825-1893