HPI
- Patient is a 30 y.o. man with known HIV disease on HAART who presents with a 2 week history of right sided foot drop, lethargy, confusion and short term memory loss.
- Most recent CD4 count 84, HIV viral load undetectable.

Pertinent Physical Exam Findings
- Somnolent; oriented to person and place
- Constructional apraxia
- Slow rate of speech
- LLE: 5/5 strength through out
- RLE: IO 4+, IP 2, Ham 3, TA 0, Gastroc 2, EHL 1
- Cranial nerves, coordination and sensation intact
DIFFERENTIAL DIAGNOSIS FOR OUR PATIENT

- Progressive Multifocal Leukoencephalopathy
- HIV Encephalopathy
- Primary CNS Lymphoma
- Toxoplasmosis
We need a framework to guide our clinical decision making while assessing our patient.
ALGORITHM FOR MANAGEMENT OF HIV PATIENTS WITH CNS SYMPTOMS

HIV Patient with CNS Symptoms (CD4 count and Viral Load)

Lesion with Mass Effect

CT/MRI

Lesion without Mass Effect

Impending Herniation

Steroids and Surgical Decompression

Toxo Serology and PPx

Safe to LP

CSF

Safe to LP

Anti-toxo Trial

Specific Rx

Biopsy

CSF

Specific Rx

CSF

Improvement after Two Weeks

Continue Rx

Safe to LP

Conclude

Continue Rx

Specific Rx
OUR PATIENT’S DIFFERENTIAL DIAGNOSIS

- Progressive Multifocal Leukoencephalopathy
- HIV Encephalopathy
- Primary CNS Lymphoma
- Toxoplasmosis

Let's begin by discussing PML…
Originaly described in patients with lymphoproliferative, myeloproliferative diseases and solid organ transplants.

- Caused by reactivation of Polyomavirus JC.

- Primary infection is asymptomatic and occurs in childhood, 86% of adults have positive antibodies.

- Virus remains latent in kidneys and bone marrow.

- Reactivation leads to lytic infection of oligodendrocytes in the CNS using the 5HT2a receptor.

- Reactivation tends to occur at CD4 <200, but can occur at any level of immune suppression.
• AIDS has caused the incidence of PML from 0.15 cases per million to 0.6 cases per million.

• In the current HAART era the prevalence has fallen to 0.3-1% from 1-5% in all HIV infections.

• AIDS accounts for nearly 86% of all cases of PML.

• After HIV/AIDS the major causes of PML lympho and myeloproliferative disorders, solid tumors, congenital immunodeficiencies and immune suppression with steroids.

• There is an increasing incidence of PML associated with anti-TNF pharmaceuticals.
Before reviewing our patient’s imaging let us review the relevant imaging modalities and the normal brain anatomy as it appears on MRI.
IMAGING MODALITIES FOR THE BRAIN

- **CT**: Image reflects the density of tissues in the area of interest, good for assessing bone.
- **MRI**: Signal intensity derives from tissue water and lipid content.
  - Increased water and reduction of lipids:
    - Increases T2 signal
    - Decreases T1 signal
  - FLAIR sequence is a T2 acquisition with suppression of CSF for better visualization
  - Areas of slow fluid diffusion result in:
    - Hyperintensity on DWI
REVIEW OF NORMAL BRAIN ANATOMY ON MRI

Axial FLAIR

- R Temporal lobe
- Pons
- Cerebellar Hemisphere
- Vermis
- Cerebral Peduncle
- Middle Cerebellar Peduncle
- Right Gyrus Rectus
- Colliculus
- Red Nuclei
- Occipital Lobe

L Temporal lobe
NORMAl BRAIN ANATOMY

Axial FLAIR

- Head of Caudate
- Post. Limb of Internal Capsule
- Choroid Plexus
- Ant. Limb of Internal Capsule
- Putamen
- Insula
- Pre-central Gyrus
- Thalamus
- Central Sulcus
- Lateral Ventricle
- Corona Radiata
- Parietal Lobe
- Occipital Lobe
CHARACTERISTICS OF PML LESIONS

- PML lesions appear as
  - asymmetric
  - well defined
  - Multi-focal white matter lesions
  - in no vascular territory
  - no mass effect
CHARACTERISTICS OF PML LESIONS IN VARIOUS IMAGING MODALITIES

CT: Low sensitivity and specificity
- Lesions show multifocal regions of signal hypodensity compared to surrounding white matter.

MRI: High sensitivity, but low specificity
- T1 w/o Contrast: Lesions appear with low signal intensity.
- T1 w/ Contrast: Lesions do not enhance.
- T2: Lesions appear with high signal intensity.
- T2 FLAIR: Lesions appear with high signal intensity.
- DWI: May see enhancement at leading edge.
Now to our patient’s imaging at the time of presentation.
Hypodensity is seen in the splenum of the corpus callosum as well as in the Centrum Semiovale of the Left Hemisphere. No mass effect or hemorrhage is seen.
High T2 signal intensity is seen in the **Splenum of the Corpus Callosum** extending to the **left occipital white matter and periventricular area**. This territory is larger than that observed on CT. Hyperintensity is also observed in the **left frontal pole** not previously seen on CT. Additional lesions are seen in the **left centrum semiovale**, **right** and **left frontal cortex**.
Enlargement showing characteristic U fibers seen in PML lesions. These lesions respect the gray white junction and outline the cortical invaginations expanding into the subcortical white matter.
Demonstration of the same PML lesions seen on various MRI modalities. The lesion is seen to be hypointense on T1 and does not enhance with contrast. It is hyperintense on T2 and FLAIR. DWI shows low signal intensity indicative of an older lesion.
Now with MRI findings suggestive of a demylenating process we will examine our patient’s CSF to arrive at a diagnosis.
Our Patient’s CSF

- T. Gondii DNA: not detected
- Cytomegalovirus DNA: not detected
- Viracella DNA: not detected
- HSV 1 and 2 DNA: not detected
- **JC Virus DNA:** detected

- This test has a sensitivity of 85% and a specificity approaching 100%.
- JCV DNA in the peripheral blood is found in 10-60% of PML patients and 20% of immunocompromised controls.
Having diagnosed our patient with PML and optimized his HAART regimen we will examine how his lesions have changed over time.
OUR PATIENT AT 9 MONTH FOLLOW UP

Axial FLAIR

Time of Presentation

9 Months Later

The lesion in the corpus callosum has decreased in size while the lesions in the left centrum semiovale and frontal lobes remain stable.
There has been atrophy of the periventricular white matter in the left hemisphere with enlargement of the lateral ventricle while the lesions in the left centrum semiovale and frontal lobes remain stable.
We now have several companion cases to demonstrate the variety of morphologies PML lesions may present with and how they can be observed to change over time.
There is high signal intensity in the right temporal lobe as well as high signal intensity in the temporal lobe adjacent to the right temporal horn of the lateral ventricle as well as a lesion seen in the right frontal lobe abutting the genu of the corpus callosum. No hemorrhage or mass effect is seen.
There has been expansion of the lesion in the right temporal lobe as well as extension of the right frontal lobe lesion caudally to the level of the midbrain. The right frontal lobe lesion has expanded laterally, but is still seen to respect the boarder of genu. The lesion surrounding the right temporal horn of the lateral ventricle remains largely unchanged.
There is a large confluent hyperintense lesion in the left frontal lobe as well as a second lesion in the left frontal lobe and smaller lesions near the left temporal horn of the lateral ventricle and in the right frontal lobe. No hemorrhage or mass effect is seen.
There are focal hyperintensities seen in the left parietal lobe as well as hyperintensities seen in the right parietal lobe and a larger confluent lesion in the left frontal lobe.
There is another variant of PML that presents with findings consistent with active inflammation. The pathology of inflammatory PML as well as a companion patient with these findings are to follow.
INFLAMMATORY PML

- Variant of PML that can occur after initiation of HAART.
- Characterized by worsening of symptoms soon after starting therapy.
- Result of the Immune Reconstitution Inflammatory Syndrome (IRIS).
- Robust immune response against infected oligodendrocytes results in breakdown of the BBB and edema.
  - Observed as enhancement with gadolinium and possible mass effect.
- Outcomes are more favorable with fewer long-term sequelae.
  - But mortality can be as high as 35% in these patients.
T2 and FLAIR images showing increased signal density in the left middle cerebellar peduncle. This was a primary CNS lymphoma that the patient had prior to development of PML. Additionally there is a large high signal intensity throughout the entire right centrum ovale, new at the time of presentation.
T1 pre-contrast image demonstrates areas of hypo and isosodensity in the areas identified on T2 imaging as a CNS lymphoma.

T1 post-contrast imaging demonstrates multifocal punctuate hyperintensities in the right centrum ovale. This enhancement as well as the shift of midline structures suggest these are areas of active demyelinating inflammation.

PML was confirmed by biopsy to rule out spread of the lymphoma.
Our companion patient with Inflammatory PML underwent biopsy to confirm this diagnosis. We shall look at some representative histology to highlight the major findings.
Brain biopsy demonstrating oligodendrocytes with enlarged basophilic nuclei with eosinophilic inclusions and macrophage invasion of the tissue seen on PAS staining.

Immunohistochemical staining of oligodendrocytes for JC virus proteins.
Brain biopsy remains the gold standard for diagnosis of PML. It is, however, an invasive procedure associated with significant morbidity. There has been a good deal of effort to develop new methods of confirming the diagnosis that are non-invasive. MRI Spectroscopy is one such approach.
- High Choline and Creatine levels and ratio are indicative of demyelination.

- The NAA/Cr ratio is lower in PML than HIV encephalopathy.

- Elevated lipid levels are indicative of necrotic lesions.

Having explored PML at length let us return to our differential diagnosis in order to understand the presentation and imaging findings of these other illnesses.
DIFFERENTIAL DIAGNOSIS

- Progressive Multifocal Leukoencephalopathy
- HIV Encephalopathy
- Primary CNS Lymphoma
- Toxoplasmosis
CHARACTERISTICS OF HIV ENCEPHALOPATHY

Patients present with:
- Subcortical Dementia
  - Memory and psychomotor speed impairment
  - Depression
  - Movement disorders

On MRI lesions are:
- Symmetric
- Poorly demarcated
- Confluent
- Periventricular
- No observed mass effect

Laboratory studies reveal:
- Elevated levels of HIV RNA and proteins in the CSF
Symmetric hyperintensities seen in both cerebral hemispheres. The lesions are not noticeable on T1 helping to distinguish this from PML.
DIFFERENTIAL DIAGNOSIS

- Progressive Multifocal Leukoencephalopathy
- HIV Encephalopathy
- Primary CNS Lymphoma
- Toxoplasmosis
CHARACTERISTICS OF PRIMARY CNS LYMPHOMA

Patients may present with:
- Focal neurological deficits
- Neuropsychiatric symptoms
- Seizure
- Headache (late)
- Visual hallucinations

On MRI lesions are:
- Hyperintense on T1 and T2
- Diffusely contrast enhancing
- Involve both cortical and subcortical structures
- Moderately edematous with observed mass effect

Laboratory studies reveal:
- Positive CSF cytology
- Epstein-Barr virus RNA in the CSF detected by PCR
  - Near 100% Sensitivity and Specificity
Single hyperintense mass with poorly demarcated boarders and surrounding edema. The lesion is **contrast enhancing** and is shown to be **well circumscribed**. Location of lesions can aid in distinguishing from PML. Biopsy, when possible, is very helpful in making the diagnosis.
DIFFERENTIAL DIAGNOSIS

- Progressive Multifocal Leukoencephalopathy
- HIV Encephalopathy
- Primary CNS Lymphoma
- Toxoplasmosis
CHARACTERISTICS OF TOXOPLASMOsis

Patients may present with:
- Headache
- Fevers
- Focal neurological deficits
- Seizures
- Encephalopathy

On MRI lesions are:
- Multiple
- Hyperintense
- Ring enhancing with contrast
- Show predilection for the Basal Ganglia

Laboratory studies reveal:
- Seropositive for T. gondii antibodies
TOXOPLASMOSIS

The Pre-contrast image demonstrates a single hyperintense lesion with surrounding edema producing a local mass effect. The post-contrast image demonstrates that the lesion is ring enhancing.
Next let's talk about treating PML...
TREATMENT

- No re-myelination patients have permanent neurologic sequela.
- Initial symptom severity may lessen as edema and inflammation resolve.
- Since the development of HAART the mortality of PML has dropped from 90% in the first 3 months to 50%.
- No specific treatment, HAART is the only method shown to slow disease progression.
- Steroids for IRIS-PML.
- Trials of Mitrazapine, Cytarabine, Cidofovir, Interferon-2b have all failed to show improvement of symptoms.
- Investigations of Mefloquine is underway.
SUMMARY

- PML is a rare, but serious complication of HIV/AIDS.
- Lesions progress quickly, with lifelong sequelae.
- MRI is the preferred modality for assessing many brain lesions.
- Patterns of demyelination, edema, mass effects and contrast enhancement along with serologic testing can be used to arrive at a diagnosis without biopsy.
- There is no specific treatment, but life expectancy has improved with HAART.
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REFERENCES


