Radiologic evaluation of progressive multifocal leukoencephalopathy (PML) in a patient with congenital HIV infection

Christopher Doughty, MSIII
Gillian Lieberman, M.D.
Core Radiology Clerkship
Beth Israel Deaconess Medical Center
Our Patient: ED Presentation

- 20 y/o male h/o congenital HIV, off HAART >1 year – “didn’t feel like taking the meds anymore”
- Presents to ED from clinic appointment with question of intoxication or suicidality
- In ED, also complains of R leg weakness, worsening over 1.5 months
  - Difficulty walking – foot catches floor
- Complains of slowed speech for 5-6 months
- Admitted, section 12
  - Later, determined not to be suicidal. Possible misunderstanding in clinic/ED?
Our Patient: History

- PMH: congenital HIV, no known opportunistic infections
- Meds: none; off HAART 1 year
- Allergies: none
- SH: lives with friends, no contact with family; recently fired from job; occasional cigarettes and marijuana
- ROS: negative
Our Patient: Physical Exam

- Mental Status: slowed speech; minor inattention; recalls 2/3 words at 2 minutes
- Motor: Weakness of R hip flexors, hamstrings, foot dorsiflexors, toe extensors
- Reflexes: R patellar brisk, R toe upgoing
- Coordination: Slow rapid alternative movements bilaterally
Our Patient: Forming a Differential

- Localize the Lesion Clinically
  - Pattern of R leg weakness, brisk reflex, and upgoing toe suggest upper motor neuron lesion: spinal cord or above
  - Cognitive difficulties are not caused by spinal cord lesions
  - Process must involve the brain

- Time Course
  - Subacute – stroke, e.g., unlikely
Our Patient: Importance of HIV

- 40% of AIDS patients develop significant neurological symptoms! (Ciricillo & Rosenblum)
- The progression of his disease will influence our differential diagnosis
- Our patient’s labs:
  - CD4 count: 33
  - Viral load: 36,000
Our Patient: Possible Opportunistic Infections

Our patient’s CD4: 33

Key: Cry, Cryptococcus; NHL, Non-Hodgkin’s lymphoma; DEM, AIDS dementia; PML, Progressive multifocal leukoencephalopathy; Tox, Toxoplasmosis; CMV, Cytomegalovirus

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Our Patient: Differential Diagnosis

- Toxoplasmosis
- Primary CNS lymphoma or systemic lymphoma with CNS involvement
- PML
- Brain abscess – bacterial, TB
- TB granuloma in the brain
- CMV encephalitis
- Cryptococcus - Cryptococcoma
- HIV encephalitis
- Subdural hematoma
- Metastasis

Most common causes of focal CNS lesions in AIDS patients
Proper Radiologic Assessment of the Brain

- CT or MRI
  - American College of Radiology (ACR) appropriateness criteria: both have a role
    - CT w/o contrast – screening for acute hemorrhage
    - MRI w/ and w/out contrast – screening for infections and masses
  - MRI is more sensitive for the top three focal lesions in AIDS patients: Toxoplasmosis, Lymphoma, and PML (Ciricillo & Rosenblum)
Normal Head CT

Gray Matter is more dense than White Matter.

Deep Gray Matter (Caudate Nucleus)

CSF

Thalamus

Choroid Plexus (Calcifications)

Bone

axial view, c-

www.migraine-aura.org
Our Patient: Head CT, w/o contrast

What do you see?
Continue to see findings
Our Patient: Focal low density areas on CT

Focal, low density regions

axial view, c- PACS, BIDMC
Our Patient: Focal low density areas on CT
Our Patient: Focal low density areas on CT
We’ve found multiple, focal, low density areas in our patient’s head CT w/out contrast. Let’s look at two companion patients for examples of two important findings we DON’T see in our patient.
Companion Patient 1: Acute Hemorrhage on CT

Clearly, there is no evidence of hemorrhage in our patient’s CT.
In this patient, the low density lesion is exerting mass effect on the lateral ventricle. The calcification within the choroid plexus has been displaced and the ventricle has shifted toward the midline.
Companion Patient 2: More Mass Effect on the Ventrices on Head CT

Looking superiorly in the brain, we see further evidence that the lateral ventricle is being displaced.
Companion Patient 2: Midline Shift on Head CT

Here we see that the lesion has actually shifted the midline of this patient’s brain 2.93mm to the right.

This patient has Toxoplasmosis.
Our Patient: No Evidence of Mass Effect on Head CT

There is no evidence of mass effect in our patient’s CT – the ventricles appear normal and the midline has not shifted.
We’ve found multiple, focal, low density areas in our patient’s head CT with no evidence of acute hemorrhage or mass effect. Let’s move on to MRI to learn more about our patient’s brain.
MRI of the Brain: Basics

- MRI: more sensitive; more detail of white matter and gray matter structures

T1

T2

axial views w/ out contrast

CSF is black

CSF is white

www.mr-tip.com

med.harvard.edu
MRI of the Brain: FLAIR

- FLAIR: Fluid-attenuated inversion recovery

CSF is white
All other fluid remains white

Fluid = PATHOLOGY

axial views w/out contrast

CSF is subtracted, appears black

med.harvard.edu

www.radiologyteacher.com
Our patient had leg weakness. Let’s exploit the level of detail offered by MRI to review the corticospinal tract that delivers motor information to the body from the brain so we know where to look for possible lesions.
Anatomy Review – Motor Cortex

The corticospinal tract

Axial view, T1, c-

Precentral gyrus: motor cortex

Central sulcus

med.harvard.edu

Courtesy of Dr. Bernard Chang
The corticospinal tract
Anatomy Review – Internal Capsule

The corticospinal tract

axial view, T1, c-

putamen

caudate head

internal capsule

thalamus

med.harvard.edu

Courtesy of Dr. Bernard Chang
axial view, T1, c-

suprasellar cistern

infundibulum

parahippocampal gyrus

cuneus

vertical view, T1, c-

The corticospinal tract

cerebral peduncle

internal carotid artery

med.harvard.edu

Courtesy of Dr. Bernard Chang
Anatomy Review – Pons

The corticospinal tract

axial view, T1, c-

maxillary sinus
prepontine cistern
cavernous sinus
pons
vermis
falx cerebri

med.harvard.edu

Courtesy of Dr. Bernard Chang
Anatomy Review – Medullary Pyramids

The corticospinal tract

Axial view, T1, c-

Pyramid
Vertebral artery
Inferior olive

 Courtesy of Dr. Bernard Chang

med.harvard.edu
Now that we have reviewed the corticospinal tract, let’s look at our patient’s MRI findings.
Our patient: MRI

FLAIR, axial view  T2, axial view

What do you see? Continue to view findings
Our patient: Hyperintense foci

FLAIR, axial view

T2, axial view

Several hyperintense lesions on T2 and FLAIR
Our patient: Multiple Hyperintense foci

FLAIR, axial views

Several T2 hyperintense lesions

Thalami

PACS, BIDMC
Our patient: Hyperintense foci in the brainstem

FLAIR, axial views

- L Pons
- L Middle Cerebellar Peduncle

Several T2 hyperintense lesions

PACS, BIDMC
Our patient: pre- and post-contrast MRI

T1 Pre-Contrast, axial view

T1 Post-Contrast, axial view

No enhancement
Upon viewing our patient’s MRI, we’ve found several hyperintense foci throughout the bilateral subcortical white matter, the bilateral thalami, the L pons, and the L middle cerebellar peduncle. These lesions did NOT enhance.

Let’s look at MRI findings from two other companion patients to see why we looked for contrast enhancement.
Companion Patients 3 and 4: Ring-Enhancing Lesions on MRI

Companion patient 3
T1 post-contrast, axial view

Companion patient 4
T1 post-contrast, axial view

Primary CNS Lymphoma

Toxoplasmosis

Lorberboym, et al.
PACS, BIDMC
Ring-Enhancing Lesions: DDx

- There is a large differential for ring-enhancing lesions in AIDS patients!
  - Toxoplasmosis
  - Primary CNS lymphoma or systemic lymphoma with CNS involvement
  - Brain abscess – bacterial, TB
  - TB granuloma in the brain
  - CMV encephalitis
  - Cryptococcus – Cryptococcoma
  - Metastases
Because the lesions we saw in our patient’s MRI did not enhance, we have eliminated many items from our original differential—those that tend to show ring-enhancement.
Our Patient: Original Differential

- Toxoplasmosis
- Primary CNS lymphoma or systemic lymphoma with CNS involvement
- PML
- Brain abscess – bacterial, TB
- TB granuloma in the brain
- CMV encephalitis
- Cryptococcus - Cryptococcoma
- HIV encephalitis
- Subdural hematoma
- Metastasis
Our Patient: Remaining Differential

- PML
- HIV encephalitis
Our patient: Summary of Findings

- Multifocal low-density lesions on CT without mass effect
- Multiple, focal, subcortical white matter T2 hyperintense lesions
- Additional T2 hyperintense lesions in thalami, pons, and middle cerebellar peduncle
- Hypointense to white matter on T1; no enhancement with gadolinium
PML: Classic Findings

- Multifocal low-density lesions on CT without mass effect
- Multiple, focal, subcortical white matter T2 hyperintense lesions
- 10% with brain stem or cerebellar involvement
- Hypointense to white matter on T1; no enhancement with gadolinium
The imaging findings in our patient are the classic findings for a patient with PML. Let’s look at the imaging findings from a patient with HIV encephalitis to differentiate between the two diseases, as their imaging findings can appear similar.
Companion Patient 5: HIV Encephalitis

FLAIR, axial views

PACS, BIDMC

What do you see? Continue to view findings
Our patient, for comparison

FLAIR, axial view

Focal, Asymmetric

PACS, BIDMC

PML

Companion Patient 5: Diffuse Hyperintensity

Companion Patient

FLAIR, axial view

HIV Encephalitis
Companion Patient 5: Brain Atrophy on MRI

Our patient, for comparison
FLAIR, axial view

Wide sulci

Companion Patient
FLAIR, axial view

PACS, BIDMC
HIV Encephalitis

PACS, BIDMC
Companion Patient 5: Ventricular Enlargement as a Sign of Brain Atrophy on MRI

Our patient, for comparison
FLAIR, axial view

Ventricular Enlargement

PACS, BIDMC
PML

HIV Encephalitis

PACS, BIDMC
HIV Encephalitis: Classic Findings

- **Diffuse, symmetric** T2 hyperintensity
- **Atrophy** (Proenzale & Jinkins)
  - Not always present, however
- HIV is neurotropic; infects glial cells and neurons throughout the CNS, explaining the white matter hyperintensity and atrophy, respectively, seen on MRI. (Heald)
We’ve learned that HIV encephalitis is characterized by diffuse T2 hyperintensity, rather than focal hyperintense lesions like those of PML. We also learned that atrophy is characteristic of HIV encephalitis and not PML.

Let’s learn more about PML.
PML: Progressive Multifocal Leukoencephalopathy

- An infection
- JC Virus
  - Epidemiology
    - Asymptomatic primary infection
    - 60-80% seropositive rate in American adults (Demeter)
  - Reactivated by immunosuppression (Shah et al.):
    - HIV/AIDS (79%)
    - Hematologic malignancies
    - Organ transplant
    - Natalizumab (Tysabri) – MS medication
PML: Pathogenesis

- The JC virus preferentially infects oligodendrocytes, leading to their death
  - Result: widespread CNS demyelination and reactive gliosis (Provenzale & Jinkins)
PML: Treatment and Prognosis

- **HAART** – only therapy with proven survival benefit *(Cinque et al.)*
  - Before HAART, only 10% of patients lived longer than 1 year *(Koralnik)*
  - One year survival rate now: 50% *(Koralnik)*
- The disease remains uniformly fatal, however.
Our Patient: Diagnosis

- Clinical presentation and radiologic findings are extremely suggestive of PML.
- Gold standard of diagnosis for PML:
  - Detection of JC Virus DNA in CSF by polymerase chain reaction (PCR)
    - Specificity: 92-100% (Cinque et al.)
    - Negative in our patient, however
      - Only 72-92% sensitive (Cinque et al.)
- Based on clinical and radiologic findings, our patient still presumed to have PML.
Our Patient: Result

- Our patient was restarted on HAART therapy; he was also enrolled in a local Directly Observed Therapy (DOT) program to help ensure compliance.

- His prognosis is poor, but it is hoped that HAART will slow the progression of his disease and prolong his survival.
Summary

- Tests of choice: CT, MRI
- CT: acute hemorrhage, mass effect
- Ring-enhancing lesions: wide differential
- PML: demyelinating infection, JC virus
- PML: Focal T2 hyperintensities that do not enhance
- HIV encephalopathy: Diffuse T2 hyperintensity with atrophy
Acknowledgements

- **Dr. Gul Moonis**, Assistant Professor of Radiology, Harvard Medical School
- **Dr. Rafael Rojas**, Assistant Professor of Radiology, Harvard Medical School
- **Dr. Bernard Chang**, Assistant Professor of Neurology, Harvard Medical School
References


- Demeter LM. Epidemiology of JC and BK virus infection. UpToDate 2008. www.uptodate.com


References


