Ring Enhancing Lesions in a Patient with AIDS

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Agenda

• Background: CNS complications of AIDS
• Patient presentation
• Menu of radiologic tests
• Differential diagnosis: ring enhancing lesions
• Differentiating CNS lesions
• Summary
AIDS and the CNS

- 10% of patients have neurological signs and symptoms when they first present with AIDS.
- 30-60% of patients with AIDS will develop neurological complications during the course of their illness.
- 70-90% of patients with AIDS show CNS involvement at autopsy.

Understanding and recognizing the appearance of CNS complications in patients with AIDS is important in promptly recognizing, diagnosing and initiating proper treatment.

Thurnher MM. Eur Radiol 1997;7(7):1091-7
DDx. of CNS complications of AIDS:

1. **HIV encephalitis**
2. **Opportunistic Infections:**
   - Toxoplasmosis
   - Cryptococcosis
   - CMV
   - TB
   - PML (JC virus)
   - Bacterial
   - Fungal
3. **Neoplasm**
   - Primary CNS lymphoma
   - Kaposis Sarcoma

HIV-1 Virus

http://www.niaid.nih.gov/factsheets/howhiv.htm

Thurnher MM. Eur Radiol 1997;7(7):1091-7
Index Patient – “JL”

- 49 year old man with AIDS (last CD4=17, on HAART) who presented to an OSH for unsteady gait, lower extremity weakness, headache, vomiting, dysarthria and seizures.

- PE:
  - Temp: 102.4°F
  - Multiple CN deficits

- Head CT showed **multiple ring enhancing lesions**

- Started on broad spectrum antibiotics with coverage for toxoplasma.

- No improvement → Brain biopsy: non diagnostic

- Transferred to BIDMC for further management.
Before we discuss the imaging that was obtained when JL arrived at BIDMC, let’s first review the radiologic modalities that can be used to evaluate the CNS in a patient with AIDS.
Menu of Radiologic Tests

Primary Modalities:
- CT (w/wo contrast)
- MRI (w/wo contrast)
  - T1, T2, FLAIR
  - DWI/ADC Maps

Adjunctive Modalities:
- FDG-PET
- Thallium 201 SPECT
- Special MRI protocols
  - MR Spectroscopy
  - Perfusion MR

Menu of Radiologic Tests

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• FDG-PET
• Thallium 201 SPECT
• Special MRI protocols
  – MR Spectroscopy
  – Perfusion MR

These adjunctive modalities are not used in the routine imaging or evaluation of CNS lesions in patients with AIDS. They are primarily used when the identity of a lesion is in question and additional non-invasive imaging would potentially alter treatment. PET and SPECT scanning are used most frequently. MR spectroscopy and perfusion MR are not routinely used and will not be discussed in this presentation.

Adjunctive imaging modalities will be discussed later on in the presentation.
Menu of Radiologic Tests

Computed Tomography:

Pros

1. Fast
2. Readily available
3. Can scan people with contraindications to MRI

Cons

1. Less sensitive than MRI
2. Limited evaluation of posterior fossa
3. Can miss some white matter disease
4. Brain radiation
Menu of Radiologic Tests

Magnetic Resonance Imaging:

Pros

1. Better than CT at determining if a lesion truly is solitary
2. Increased sensitivity to subtle white matter disease and posterior fossa lesions
3. May be able to identify small peripheral lesions missed by CT that are more accessible for biopsy
4. No radiation
5. Multiple imaging sequences can aid diagnosis (DWI/ADC/FLAIR)

Cons

1. More costly, less readily available

** MRI is the BEST test to assess CNS lesions

Normal T1 and T2 MRI

BIDMC, PACS

Areas of restricted diffusion appear BRIGHT on DWI

Apparent Diffusion Coefficient (ADC): The signal intensity of DWI depends on factors other than diffusion information (spin density, TR, TE). By combining multiple DWIs, these other factors can be eliminated. ADC also eliminates “T2-Shine through” on DWI caused by intense T2 signals.

Areas of restricted diffusion appear DARK in ADC

Images from Fillipi. Clinical MR Neuroimaging. pg 411
Imaging: “JL”

Axial T1WI MRI pre gadolinium

Multiple ring enhancing Lesions throughout CNS

Axial T1WI MRI post gadolinium

Images provided by Mizuki Nishino, MD; BIDMC
Looking at additional MRI sequences allows us to better characterize the center of the lesion and surrounding tissue.
Hypo/isointense lesion with ring enhancement

Enhancing lesion surrounded by hyperintense edema

Hyperintense on DWI = restricted diffusion

Hypointense on ADC = restricted diffusion

Images provided by Mizuki Nishino, MD; BIDMC, PACS
There is a well defined differential diagnosis for ring enhancing lesions in the CNS:
DDx. Ring Enhancing Lesions (*)

- **Infection:**
  - Toxoplasma
  - Cystercercosis
  - Brain abscess (bacterial, fungal)

- **Neoplasms**
  - Brain tumors/metastases
  - Primary CNS Lymphoma

- **Demyelinating Disease**
  - MS
  - ADEM

- **Vascular lesions**
  - Resolving infarction
  - Hematoma
  - Thrombosed aneurism

- **Radiation necrosis**

- **Postoperative changes**

When we consider which of these entities are common in patients with AIDS (see slide 4 for a refresher), the differential narrows, and we can focus on Toxoplasmosis, brain abscess and primary CNS lymphoma.

- Thrombosed aneurism
- Radiation necrosis
- Postoperative changes

Gamuts in Radiology, online edition
We will now explore the narrowed differential in more detail.

1. Toxoplasmosis
2. Primary CNS Lymphoma
3. Bacterial brain abscess
Toxoplasmosis: Background

- Intracellular protzoan parasite, *toxoplasma gondii*
- **Most common opportunistic infection in HIV (CD4 < 100 per \( \mu \)L)**
- Symptoms are usually secondary to **reactivation** of latent infection
- **Signs/Symptoms:** headache, fever, seizures, encephalopathy, altered mental status, neuro. deficits
- Important to quickly diagnose because **very treatable** with antibiotics
- **Toxoplasma antibody** is not always useful\(^1\)
  - Only 1/3 cases have rise in IgG
  - Only 1/2 produce antibodies in CSF
- **CSF PCR** lacks sensitivity and specificity\(^1\)
- Response to treatment is the main method of arriving at a definitive diagnosis.
- **Treatment:** Pyrimethamine and sulfadiazine or clindamycin

Toxoplasmosis: Life cycle

Cats are the main reservoirs of infection and become infected by ingesting tissue cysts. The cysts reproduce inside the feline intestinal tract.

Oocysts are shed in fecal matter and are extremely resistant to severe environmental conditions and disinfectants.

Humans become infected by either:

- Eating tissue cysts in undercooked meat
- Fecal-oral transmission from cat feces
- Blood or organ transplantation
- Transplacentally

Approximately 22.5% of people in the United States are infected.

Toxoplasmosis: Sites of Infection

- Most common sites of infection are:
  - Cortico-medullary junction
  - Basal ganglia
  - Thalamus

Image from Netter, 2004, plate 104.
Toxoplasmosis: Imaging

• CT:
  – Non-contrast: isodense to gray matter, but can be detected secondary to possible edema and mass effect
  – May be hyperdense if hemorrhagic

  – Contrast: 90% Ring-enhancement\(^1\) with is secondary to inflammatory response (patients with decimated immune systems may not show enhancement)\(^2\)

  – After treatment, can show areas of calcification

1. Koralnik, UpToDate
Toxoplasmosis: Imaging

• MRI:
  – Usually shows more lesions than CT
  – **T1WI**: hypointense or isointense to gray matter
  – **T2WI/FLAIR**: isointense or hyperintense to gray matter

  – ring enhancing, sometimes with a central focus of enhancement “target sign”.

Zimmerman, RD. Clinical MR Neuroimaging. pg 365
Toxoplasmosis Lesions

Below are 2 patients with CNS lesions that were subsequently shown to be toxoplasmosis.

Patient 1
- Head CT w/ contrast:
  - Hypodense, ring enhancing lesion and surrounding edema

Patient 2
- T2 MRI, non-contrast:
  - Hyperintense, enhancing lesion
- T1 MRI w/ contrast:
  - Hypointense, ring enhancing lesion
Primary CNS Lymphoma: Background

- Most common AIDS related neoplasm (2-5% patients)
- After Toxoplasmosis, is second most common cerebral mass lesion in AIDS patients.
- Almost always of B-cell, Non-Hodgkins type
- Likely related to EBV
- Presenting symptoms: neurological deficits, encephalopathy, seizure (similar to toxoplasmosis)
- Median survival < 1 year
- Treatment: Radiation and corticosteroids

Primary CNS Lymphoma: Sites of Infection

- Most commonly located in:
  - periventricular/periependymal white matter
  - corpus callosum

Illustrations from Netter, 2004, Plates 100, 104.
Primary CNS Lymphoma: Imaging

- **CT:**
  - Isodense to Hypodense

- **MR:**
  - **T1:** hypointense
  - **T2/FLAIR:** isointense to hyperintense

  - **Enhancement:** usually irregular enhancement or ring enhancement.
Primary CNS Lymphoma can have a wide range of appearances:
Primary CNS Lymphoma: Varying Lesions

2 different patients with lesions subsequently shown to be primary CNS lymphoma

Patient 3

T1WI +Gad.
Hypointense lesion with ring enhancement

Patient 4

T1WI +Gad.
Homogenously enhancing lesion


Right Image from Doweiko, UpToDate
Bacterial Abscess: Background

- Often presents with headache, altered mental status, nausea, vomiting, seizures, neuro. deficits due to expanding mass.¹

- Hypointense on T1, Hyperintense on T2¹
- Capsule is hypointense on T2¹
- Ring enhancing with surrounding edema¹

- Less common in AIDS patients than toxoplasmosis or primary CNS lymphoma²
  – Often associated with bacteremia

1. Fillipi, Clinical MR Neuroimaging. Pg 409
2. Koralnik, UpToDate
Bacterial Abscess: Imaging

- T1 MRI, no contrast
- T2 MRI w/ contrast
- T1 MRI +Gad

Images from Zimmerman, RD. Clinical MR Neuroimaging. pg 355
Lymphoma vs. Toxoplasmosis

Toxoplasmosis and primary CNS lymphoma are the two most common brain lesions in patients with AIDS, but, as has been shown, both can have very similar clinical features and appearance on CT and MRI.

The definitive diagnosis is usually provided by brain biopsy, but biopsy is not a benign procedures and is associated with possible morbidity and mortality. (8.4% morbidity, 2.9% mortality)¹

Delay in diagnosis while waiting to see if a patient responds to initial therapy is a significant problem:²
- lesions can rapidly progress.
- unnecessary therapies are associated with unnecessary toxicity.
- Incorrect initial treatment may result in a biopsy that could have potentially been prevented.

¹ Doweiko, UpToDate
² Fillipi, Clinical MR Neuroimaging. Pg 420
Lymphoma vs. Toxoplasmosis: Patient 5

Contrast head CT of a 38 year old woman with AIDS and a ring-enhancing lesion presumed to be toxoplasmosis.

The lesion has significantly increased in size over 2 weeks.

Same patient’s contrast head CT after 2 weeks of anti-Toxo antibiotics and no improvement. Biopsy 2 days later confirmed primary CNS lymphoma.

The appearance of a CNS lesion may give clues as to the diagnosis:
Lymphoma vs. Toxoplasmosis: Features

Favors Lymphoma

1. Large lesion size (>4 cm)
2. Extensive white matter involvement
3. Periventricular location/subependymal spread
4. Contrast enhancement along ventricular surface
5. Extension across or involvement of corpus callosum

Favors Toxoplasma

1. Large number of lesions
2. Involvement of basal ganglia
3. Hemorrhagic lesions
4. Responds to anti-Toxo drugs, usually within 7-14 days

BUT in practice, these features are unreliable in making the correct diagnosis.
Diffusion Weighted Imaging is one specific application of MRI that has attempted to distinguish ring-enhancing lesions:
Can Diffusion Weighted Imaging be used to differentiate toxoplasmosis from CNS lymphoma?

Data is inconsistent.

In general:\(^1\)

* Toxoplasmosis *tends* to be hyperintense on DWI and hypointense on ADC
  
  This corresponds with RESTRICTED DIFFUSION

* CNS lymphoma *tends* to be hypointense on DWI and hyperintense on ADC
  
  This corresponds with INCREASED DIFFUSION

BUT, there is a broad, overlapping range of diffusion values for both lesions, and both conditions can show either increased or restricted diffusion. As of now, DWI/ADC cannot accurately distinguish toxoplasmosis from CNS lymphoma.

DWI/ADC is useful for identifying **pyogenic abscesses** which are more consistently hyperintense on DWI and hypointense on ADC (restricted diffusion)

1. Fillipi. Clinical MR Neuroimaging pg 408-420
Diffusion Weighted Imaging: Examples

Patient 6: proven Bacterial Abscess

- Hyperintense on DWI
- Hypointense on ADC
- Restricted Diffusion
- Surrounded by edema

Patient 7: proven Toxoplasmosis

- Hyperintense lesion with restricted diffusion

Lesion does NOT show restricted diffusion in the center

Toxo. does not consistently show restricted diffusion, even in the same patient!

Images from Zimmerman. Clinical MR Neuroimaging pg 355, 366
Lymphoma vs. Toxoplasmosis

Nuclear medicine offers other methods for differentiating between infectious and neoplastic lesions

FDG-PET scan  Thallium 201 SPECT

Image from http://upload.wikimedia.org/wikipedia/commons/c/c6/PET-image.jpg
Patients are given trace amounts of FDG ([18F] 2-Fluoro-2-Deoxy-D-Glucose), a radioactive form of glucose that enters and becomes trapped in metabolically active cells. The concentration of FDG in tissue is directly proportional to its metabolic activity.

FDG undergoes β-decay

β-particles collide with electrons after traveling only a few mm. The collision produces 2 gamma rays which are detected and produce part of an image.

Image from http://www.biomedpet.org/howitworks.cfm
FDG-Positron Emission Tomography

FDG-PET can distinguish infectious lesions from neoplastic lesions

Toxoplasmosis/other infections:
LOW metabolic activity

Lymphoma:
HIGH metabolic activity

Lesion is hypometabolic on FDG-PET

Lesion is hypermetabolic on FDG-PET

Thallium 201 SPECT

PET scanning is not widely available and is more expensive than SPECT (Single Photon Emission Computed Tomography) because the isotopes used in PET scanning have short half-lives.

$^{201}\text{Tl}$ behaves like $\text{K}^+$ and enters living cells via the $\text{Na}^+/\text{K}^+$ ATPase. It does not accumulate in necrotic/dead tissue and thus provides another method of potentially differentiating neoplastic from infectious lesions.

$^{201}\text{Tl}$ decays via the production of single photons which can be detected and imaged.

**Patient 8:**

- T1 MRI of the brain shows an inhomogeneously enhancing lesion later shown to be CNS lymphoma at biopsy.
- $^{201}\text{Tl}$ SPECT scan shows a focal area of thallium uptake corresponding to the neoplastic lesion.

Patient “JL” -- Follow-up

• Brain biopsy at OSH was not diagnostic:
  – Few WBC
  – No bacteria/organisms via Gram stain or culture
  – No signs of lymphoma.

• Toxo antibodies negative
• Toxo PCR of CSF negative
• EBV PCR of CSF negative

• Found to have multiple abscesses throughout body and later found to be bacteremic
Patient “JL” -- Follow-up

- Widespread bacterial infection and restricted diffusion on DWI/ADC suggested abscess.
- Restarted on broader spectrum antibiotics to cover bacteria and toxoplasmosis.
- CNS lesions began to decrease in size
- Diagnosis: favored bacterial abscess, although toxoplasmosis could not be ruled out
Patient “JL”: Imaging over the course of 2 months of treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>MRI</th>
</tr>
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<tbody>
<tr>
<td>Admission</td>
<td>T1 MRI w/ Gad</td>
</tr>
<tr>
<td>s/p treatment for 1 month</td>
<td>T1 MRI w/ Gad</td>
</tr>
<tr>
<td>s/p treatment for 2 months</td>
<td>T1 MRI w/ Gad</td>
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BIDMC, PACS
Summary

- CNS complications are extremely common in patients with AIDS.

- The 2 most common CNS lesions in AIDS patients are toxoplasmosis and primary CNS lymphoma.

- Lesions are often treated empirically, but delay in definitive diagnosis can have significant consequences.

- MRI and nuclear medicine offer non-invasive methods to facilitate the identification of CNS lesions without invasive biopsy.
References


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