HIV and Progressive Multifocal Leukoencephalopathy

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Index Patient 1

- 47 y/o man recently diagnosed with HIV, presented with 2 months of change in mental status, especially word finding difficulties.
- No current antiretroviral therapy.
- On exam: predominantly frontal signs and left temporal dysfunction given his comprehension and word memory problems
- Important labs: CD4: 190, viral load 31,800.

What are the top DDX that comes to mind for this HIV+ patient?

There are many etiologies of changes in mental status, but the first/common ones to consider in an HIV+ patient with low CD4 count are:

- Toxoplasma encephalitis
- Primary CNS lymphoma
- Progressive Multifocal Leukoencephalopathy
- AIDS dementia complex
- CMV encephalitis

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In order to make our diagnosis we need further information:

- Clinical history/PE- as we discussed :
  - HIV+ with CD4 count of 190, VL of 31,800
  - progressive neurological symptoms, frontal lobe deficiencies
  - No current retroviral therapy
- Imaging studies
- Laboratory data

What do we do next?

- Since we already know the important aspects of the history and PE, lets go ahead and look at some imaging…..

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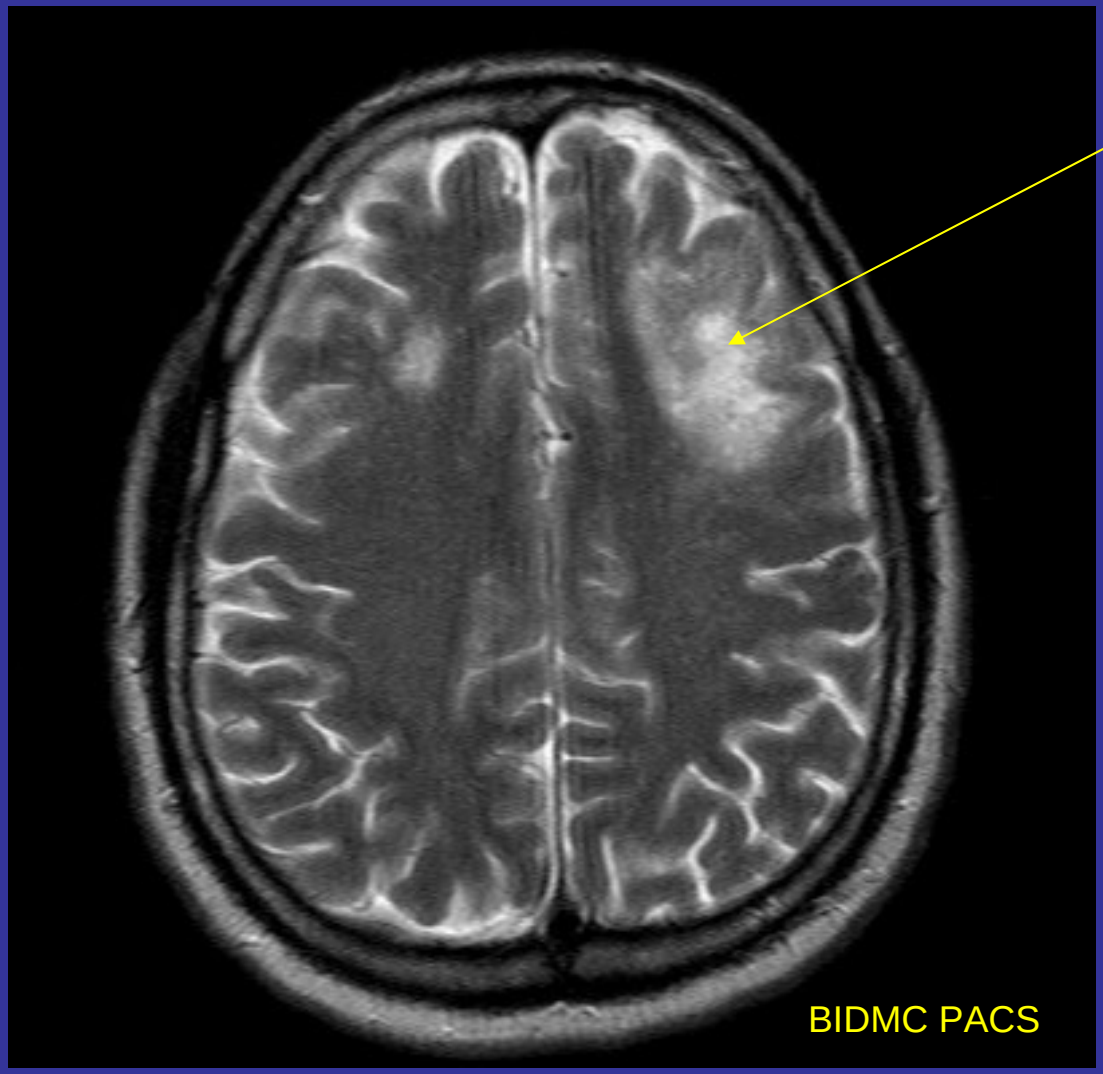
The imaging studies done: MRI#1



- There is a region of T2 signal hyperintensity.

This image can be analyzed in several modalities, for example FLAIR.

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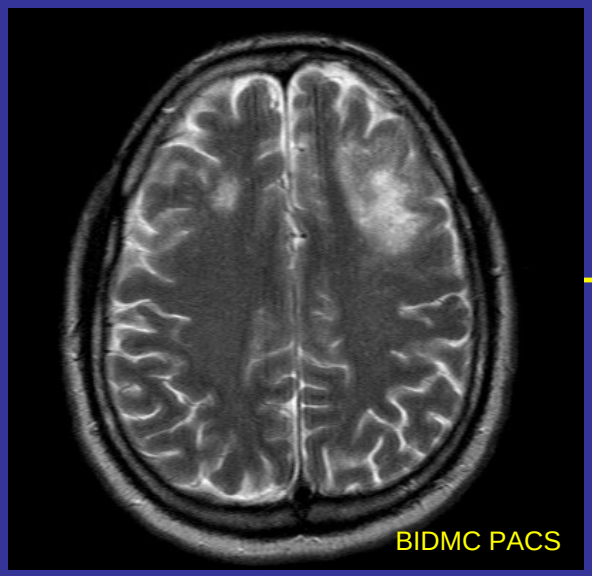
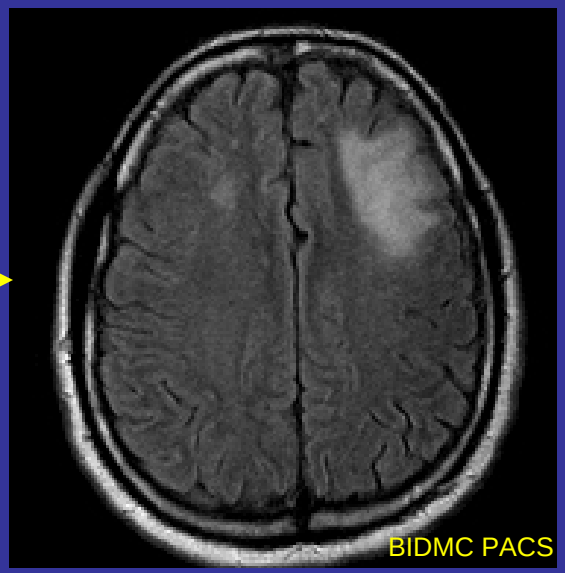
MRI #1- FLAIR (Fluid attenuated inversion recovery)

What is FLAIR? It is a T2 weighted image attenuated so that the CSF looks black. Thus it is easier to see hyperintense regions.



T2 weighted image



FLAIR

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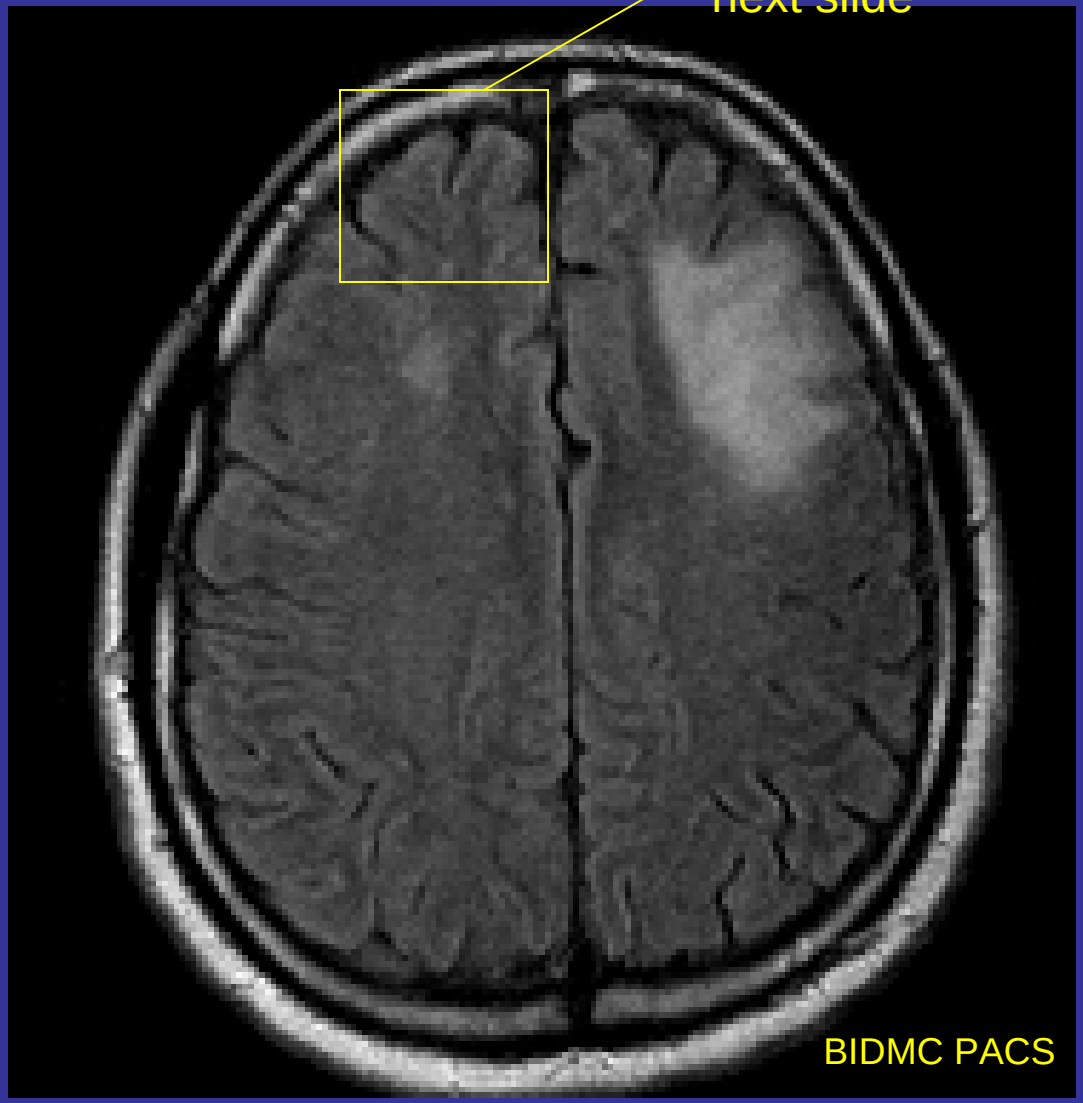
MRI#1- FLAIR

- Here, we see T2 hyperintensity within the white matter of left frontal lobe
- These changes spare the cortical gray matter. We can tell this because in T2 weighted images white matter looks darker than gray matter.



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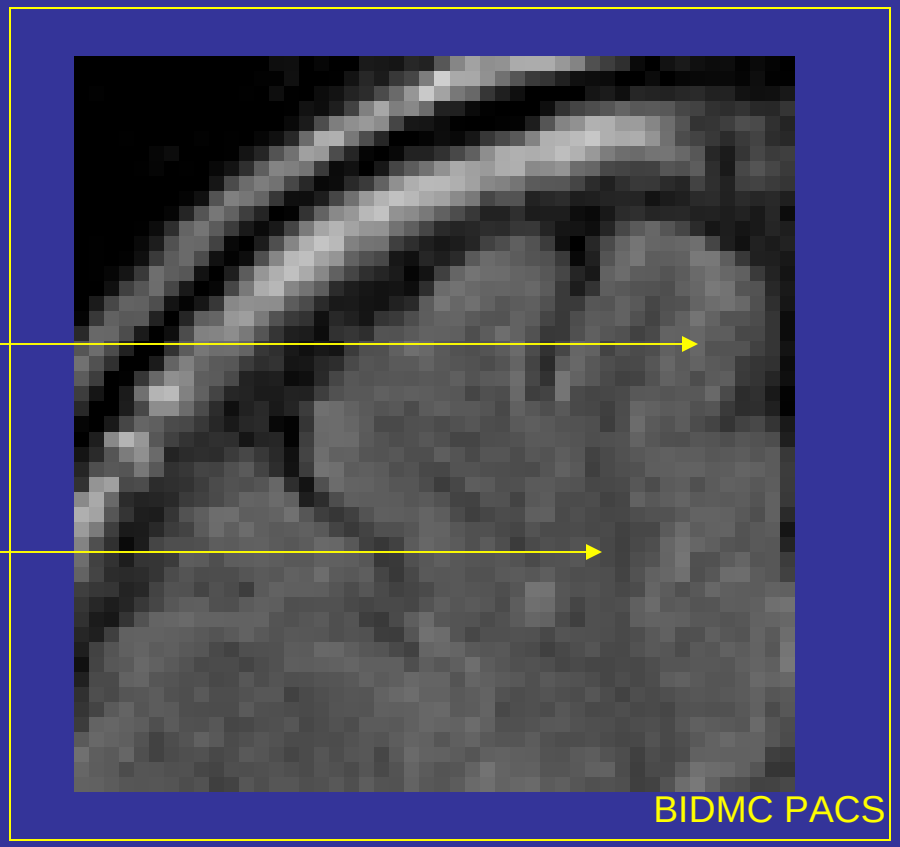
MRI- gray vs. white matter

- Here is the enlarged square from the previous image.



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Lets go over some etiologies for White matter disease of the brain on MRI- demyelinating diseases

- Common:
  - AIDS dementia complex
  - MS
  - PML
- Less common:
  - ADEM (Acute Disseminated Encephalomyelitis)
  - Acute encephalitis (rubella, measles, herpes simplex, mumps, chickenpox)
  - Vascular (small vessel disease,lacunar infarcts, aging)

Some etiologies for White matter disease of the brain on MRI- demyelinating diseases-2

- Less common-continued:
  - Trauma (white matter shearing injury)
  - Jakob-Creutzfeldt disease
  - Carbon monoxide encephalopathy
  - Malnutrition (B12 deficiency)
  - Subcortical arteriosclerotic encephalopathy (Binswanger's disease)
  - Drugs /chemotherapy/radiation therapy
  - Schilder's disease (myelinoclastic diffuse sclerosis)

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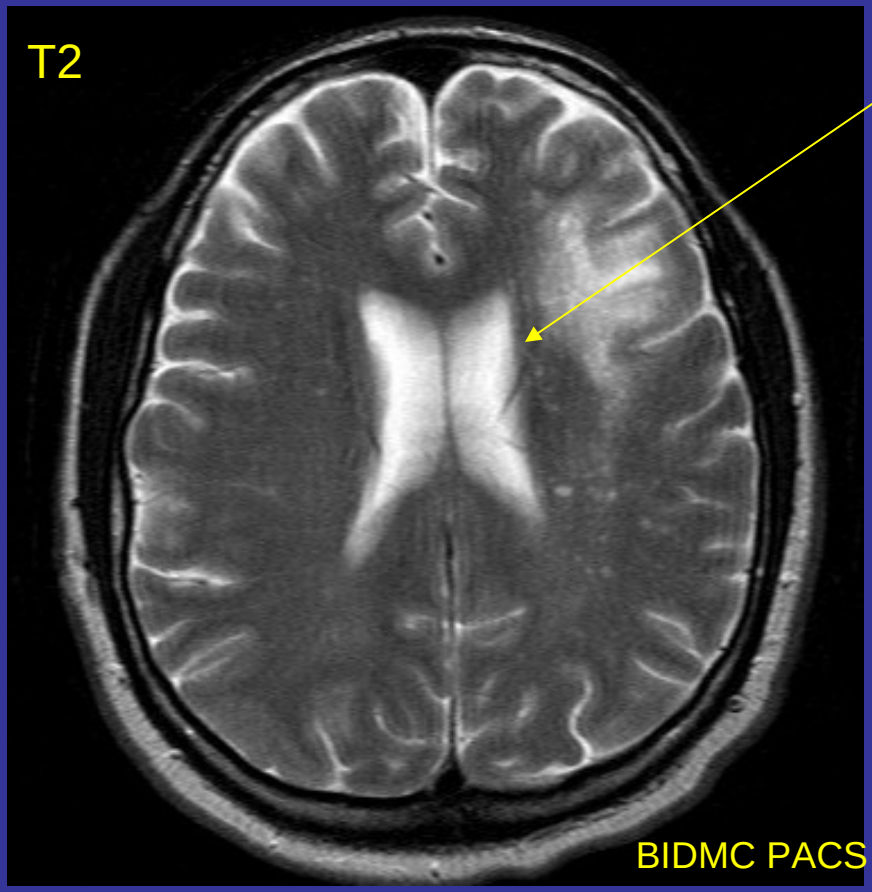
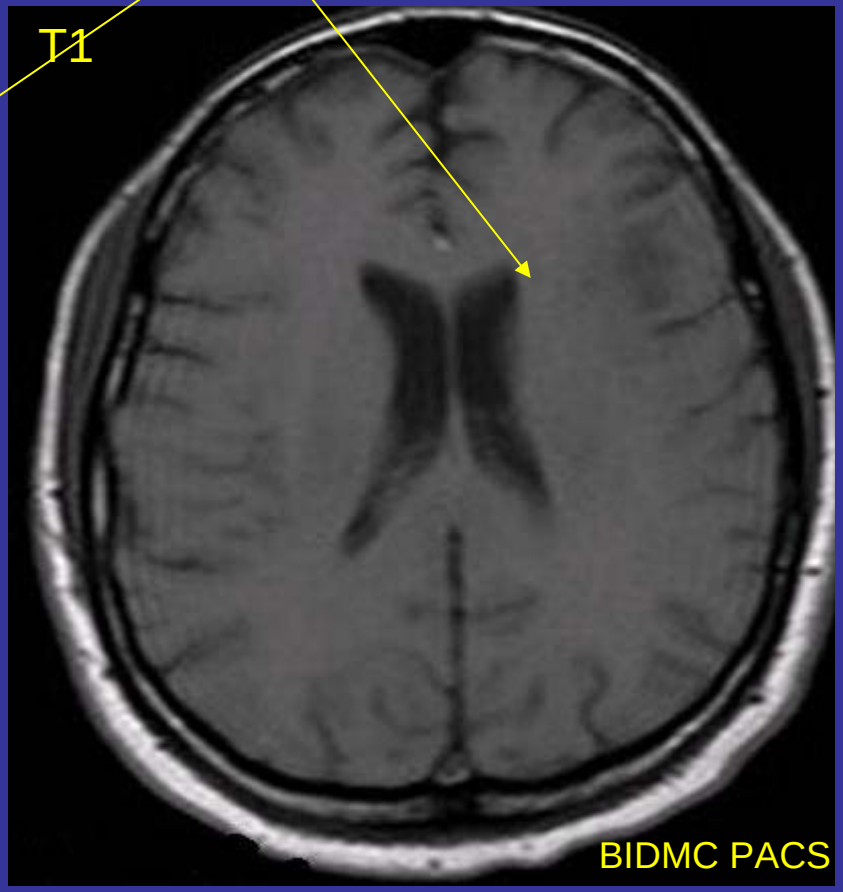
Index patient-MRI#1-mass effect

It is important also to notice that with these lesions, there is no mass effect, and no midline shift is observed





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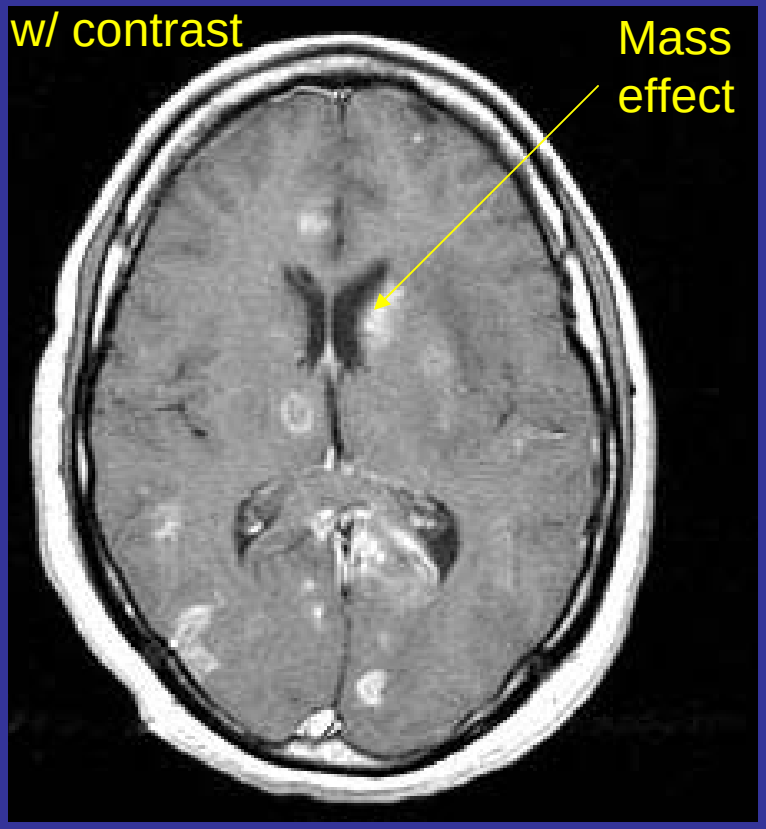
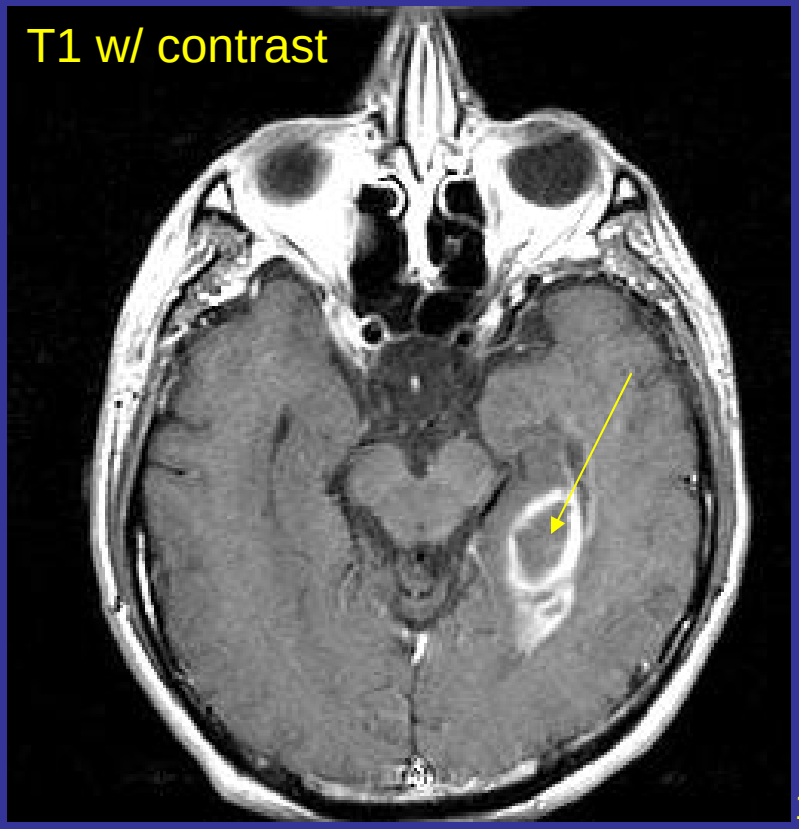
Mass effect can be an important criteria for differentiation of possible etiologies

If we see a mass effect, then we should think about differentials other than PML such as:

- Toxoplasma encephalitis



- Lymphoma



http://www.aidscience.org/neuroaids/zones/articles/1999/08/Imaging/index.asp

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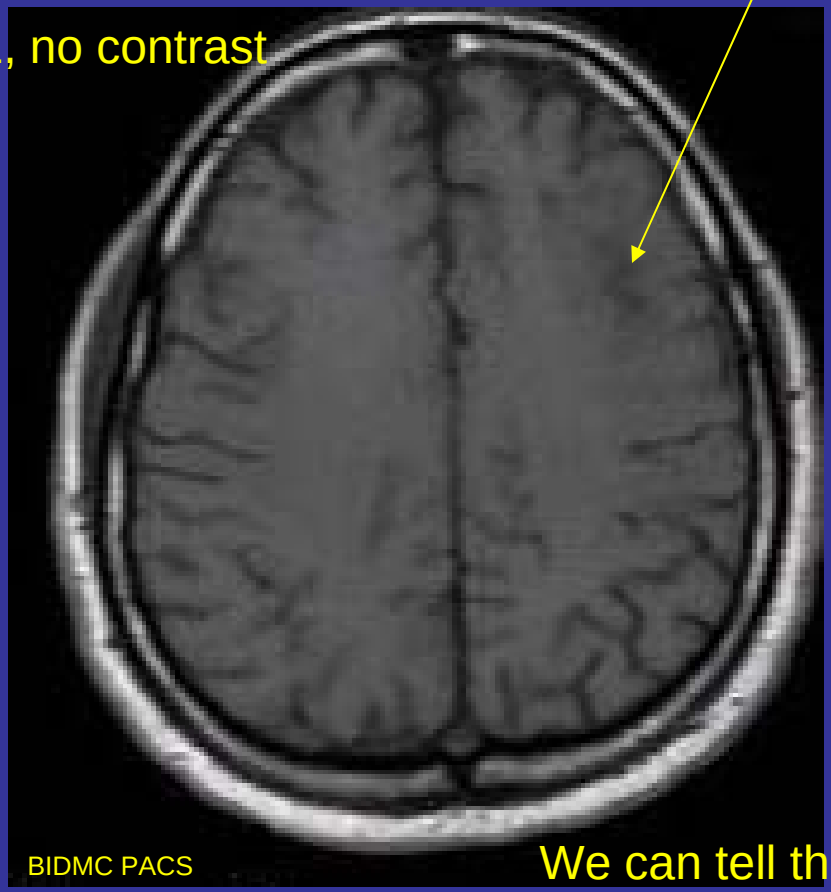
MRI-Index patient 1-contrast

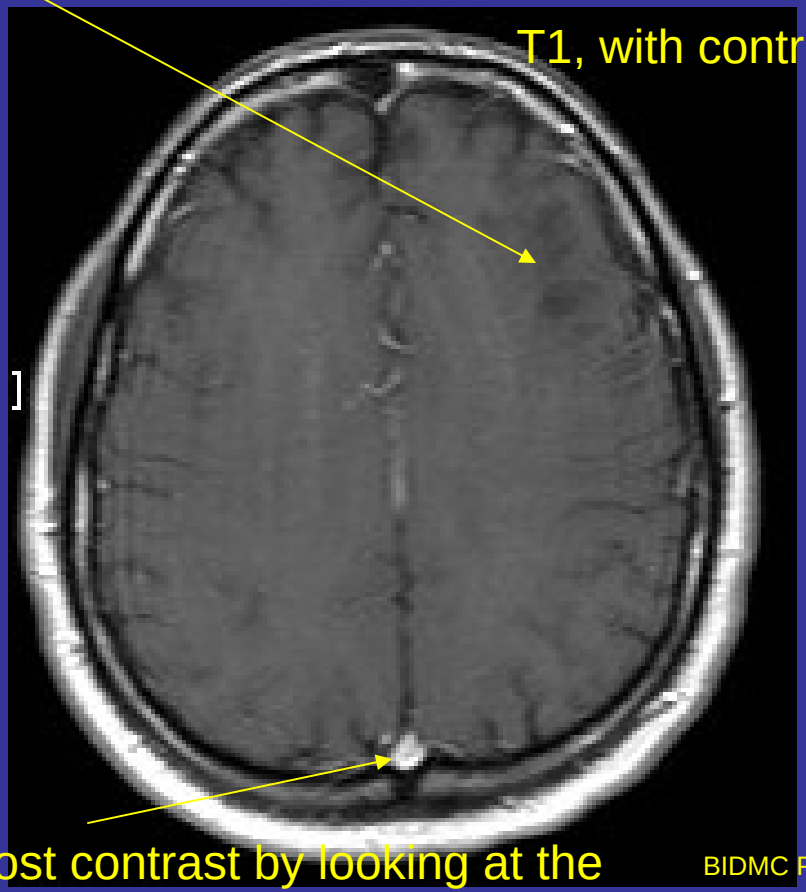
In these images of our index patient 1, we see that there are regions of T1 signal hypointensity. We also note that these regions do not enhance with contrast.

T1, no contrast



BIDMC PACS

T1, with contrast



BIDMC PACS

We can tell this is post contrast by looking at the superior sagittal sinus enhancing with contrast

Summarizing our MRI findings for Index patient 1:

- T2 hyperintensity observed, mainly within the white matter, sparing the gray matter
- There are T1 hypointense regions
- No mass effect, no midline shift observed
- No contrast enhancement observed

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Now we have our clinical history/PE and imaging findings. What next?

- Clinical history/PE
  - HIV+ with CD4 count of 190, VL of 31,800
  - progressive neurological symptoms, frontal lobe deficiencies
  - No current retroviral therapy
- Imaging
  - T2 hyperintensity observed, mainly within the white matter, sparing the gray matter
  - There are T1 hypointense regions
  - No mass effect, no midline shift observed
  - No contrast enhancement observed
- Laboratory data

Index patient 1-Lab data

- CSF:
  - HSV, EBV, toxoplasma CSF PCR were negative.
  - CSF HIV viral load was less than 200 copies/mL-this makes AIDS dementia complex less likely.
  - JC virus PCR was positive→ along with clinical picture support PML diagnosis (although CD4 at 190, and we know that PML more likely if CD4<100).
- Patient started on Combivir and Kaletra for antiretroviral therapy.

What is Progressive Multifocal Leukoencepholapathy?

- Result of infection with papovavirus-most often JC virus.
- Primary infection generally occurs during childhood and is usually clinically silent but may present as a mild respiratory illness. Infects a high proportion of the population (65% by age 14)
- During primary infection viremia occurs and the agent takes up residence in the kidney, persisting indefinitely.

What is Progressive Multifocal Leukoencepholapathy -2

- The virus becomes reactivated in immunosuppressed patients. 2-6% of HIV patients develop PML.
- Infection effects oligodendrocytes (cells responsible for myelin production) which results in white matter demyelination and reactive gliosis
- There is absence of significant inflammatory component-not much contrast uptake because of this
- Clinical symptoms: headache, motor dysfunction, visual loss, but also variable symptoms.

What is Progressive Multifocal Leukoencepholapathy-3

- Initially affects subcortical white matter within parietal and occipital lobes (although in AIDS patients, there is no specific preference).
- Subsequently involves deep white matter, usually leading to large areas of demyelination
- Lesions usually supratentorial, but in 10% of cases can find brainstem and cerebellar lesions
- There is no specific treatment of PML, but rather the treatment is to treat the immunesuppession, and reconstitute immune system.

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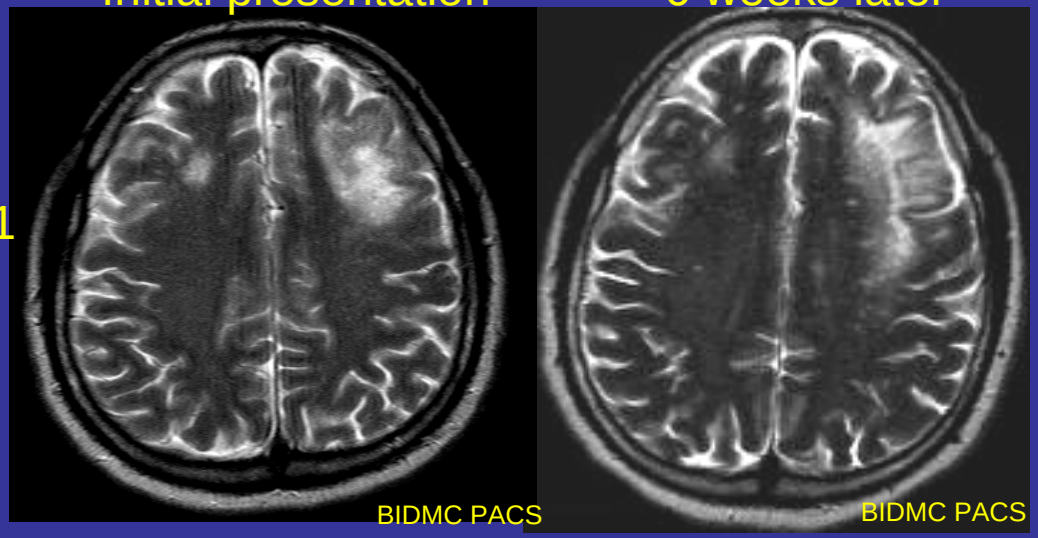
PML progresses fast, and can be fatal.

Initial presentation

6 weeks later

Index Patient 1
(AIDS patient)

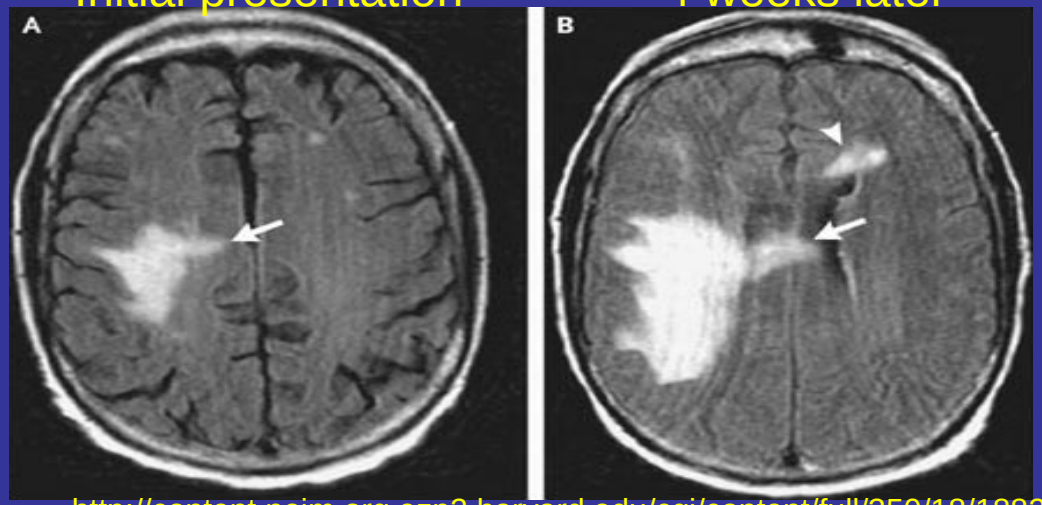


*In thinking about our HIV patient, we also need to consider immune reconstitution (see next slide)

Initial presentation

4 weeks later

Companion Patient 4 (Transplant patient)



http://content.nejm.org.ezp2.harvard.edu/cgi/content/full/350/18/1882/F2

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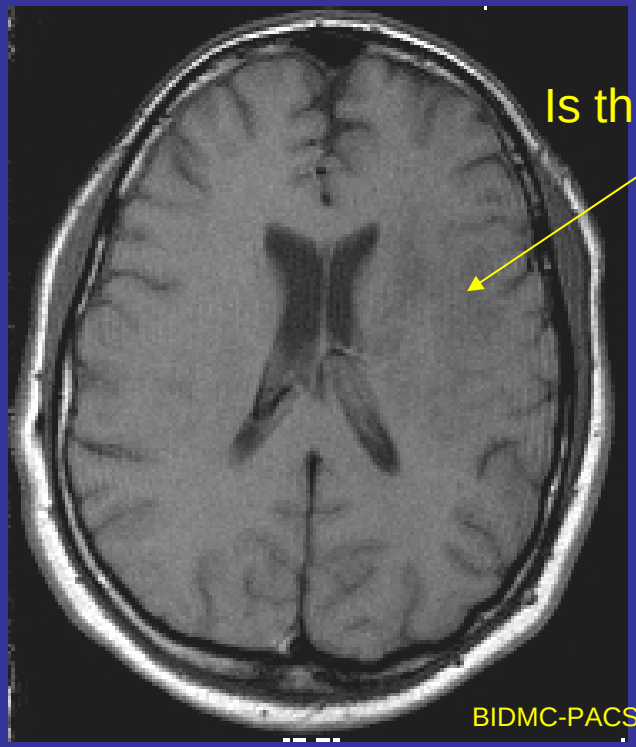
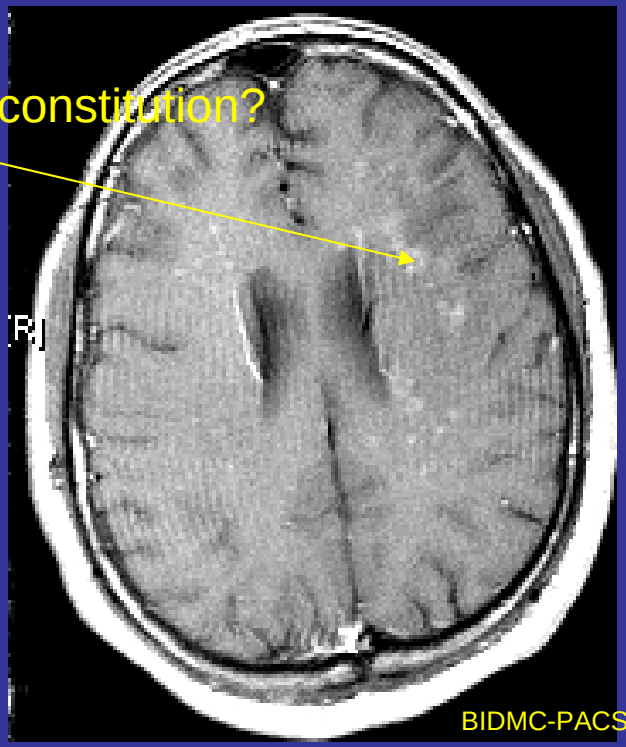
What is immune reconstitution?



Is this immune reconstitution?



The reversal of HIV-related immune system decline with therapy leads to an increase in functional CD4 cells. This immune reconstitution may trigger an inflammatory reaction in some people soon after they begin anti-HIV therapy called immune reconstitution syndrome (IRS) or immune reconstitution inflammatory syndrome (IRIS). This can often resemble an AIDS-defining illness or other condition seen in people with HIV. Although usually benign, it can sometimes be severe and/or mistaken for true disease progression.

Common radiologic findings in PML

- CT:
  - one or more hypodense nonenhancing white matter regions WITHOUT mass effect
- MR: more sensitive than CT.
  - Usually hypointense in T1, hyperintense in T2. (loss of hydrophobic myelin results in demyelination and edema, thus having increased water content)
  - Occasionally can see hyperintense on T1, hypointense in T2(thought to represent hemorrhage)
  - Usually NO contrast enhancement.
  - Findings similar to AIDS dementia complex-diagnosis made by pathological exam.

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How can one differentiate AIDS dementia Complex and PML?

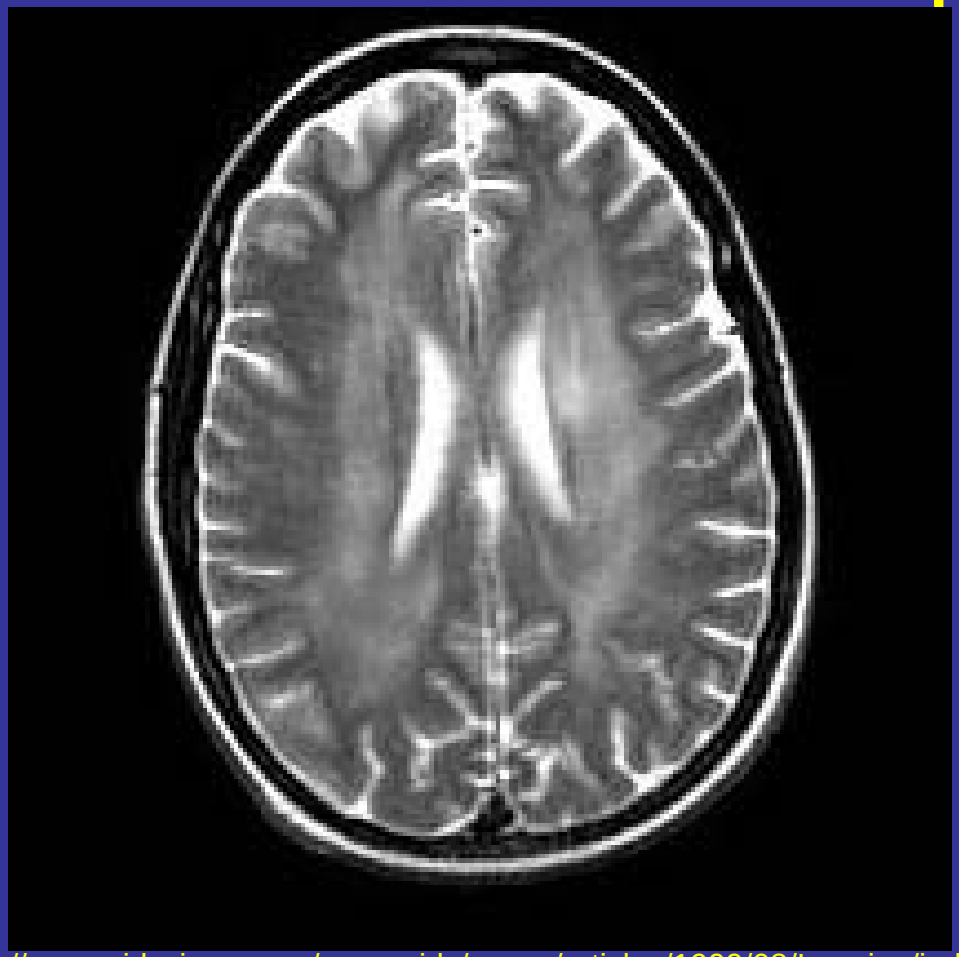

Image of a patient with AIDS dementia complex.

- Hard to differentiate between PML and ADC, but usually ADC is periventricular
- One of the important factors in pathology for ADC is HIV in the CSF, as the virus itself is responsible for the pathology. (In our patient this is unlikely the cause, since HIV in the CSF is < 200 copies/mL)
- ADC will also show widened cortical sulci and enlarged ventricles in ADC patients

http://www.aidscience.org/neuroaids/zones/articles/1999/08/Imaging/index.asp

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SUMMARY

We made our diagnosis of PML in our patient based on:

- Clinical history/PE
  - HIV+ with CD4 count of 190, VL of 31,800
  - progressive neurological symptoms, frontal lobe deficiencies
  - No current retroviral therapy
- Imaging
  - T2 hyperintensity observed, mainly within the white matter, sparing the gray matter
  - There are T1 hypointense regions
  - No mass effect, no midline shift observed
  - No contrast enhancement observed
- Laboratory data
  - CSF tests
    - JC virus PCR positive
    - HIV <200
    - Toxo, HSV , EBV were negative

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References

- Uptodate.com “Approach to HIV-infected patients with central nervous system lesions”
- Radiol Clin North Am. 1992 May;30(3):Neuroradiology of the immunosuppressed state.Davenport C, Dillon WP, Sze G.
- Radiol Clin North Am. 1997 Sep;35(5):1127-66.
Brain and spine imaging findings in AIDS patients. Provenzale JM, Jinkins JR.
- Radiol Clin North Am. 1997 Sep;35(5):1007-27.
Clinical complications of HIV infection.Heald AE, Hicks CB.
- Reeder and Felson's Gamuts in Radiology: Comprehensive Lists of Roentgen Differential Diagnosis (Hardcover) by Maurice M. Reeder, William G., Jr. Bradley
- http://www.ijri.org/articles/archives/2002-12-1/major_papers_43.htm