NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Progressive Multifocal Leukoencephalopathy (PML)

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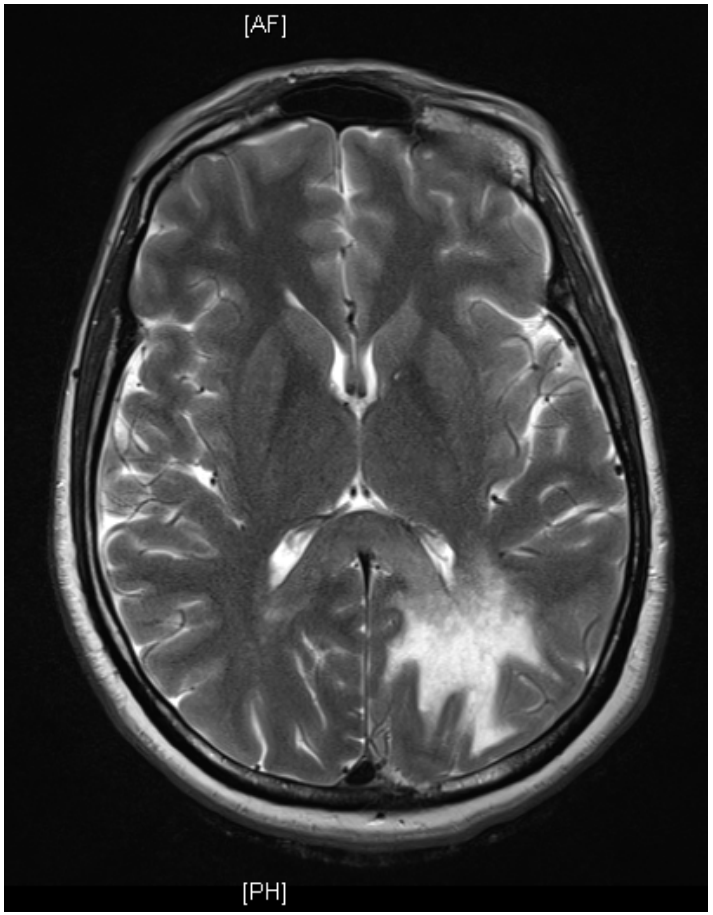
NW AETC | echo

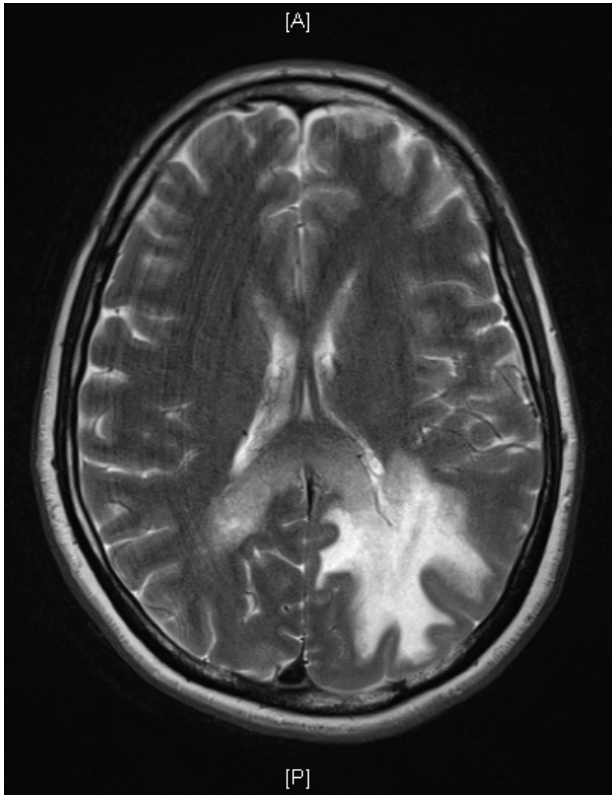
Case Presentation

- 42 yo Ethiopian woman with chronic headaches was admitted after a fall at home and complaining of R sided weakness and numbness.
- Upon arrival in the ED she was febrile and seized. HIV test was +, CD4 42, Toxo AB +. MR showed large L parietal lesion and smaller R parietal enhancing nodule



Case Presentation

- She was started on anti-toxoplasma therapy with pyrimethamine, leukovorin and sufadiazine.
- She initially improved, then worsened with fever, rash, elevated LFTs, hypereosinophila and progressive neurological symptoms. Thought to have DRESS (sulfasalazine) and an amnestic neurological reaction.
- Repeat imaging showed decreased size of R parietal lesion and increase of L parietal lesion.
- Therapy was changed to pyrimethamine + clindamycin and atovoquone (PCP)

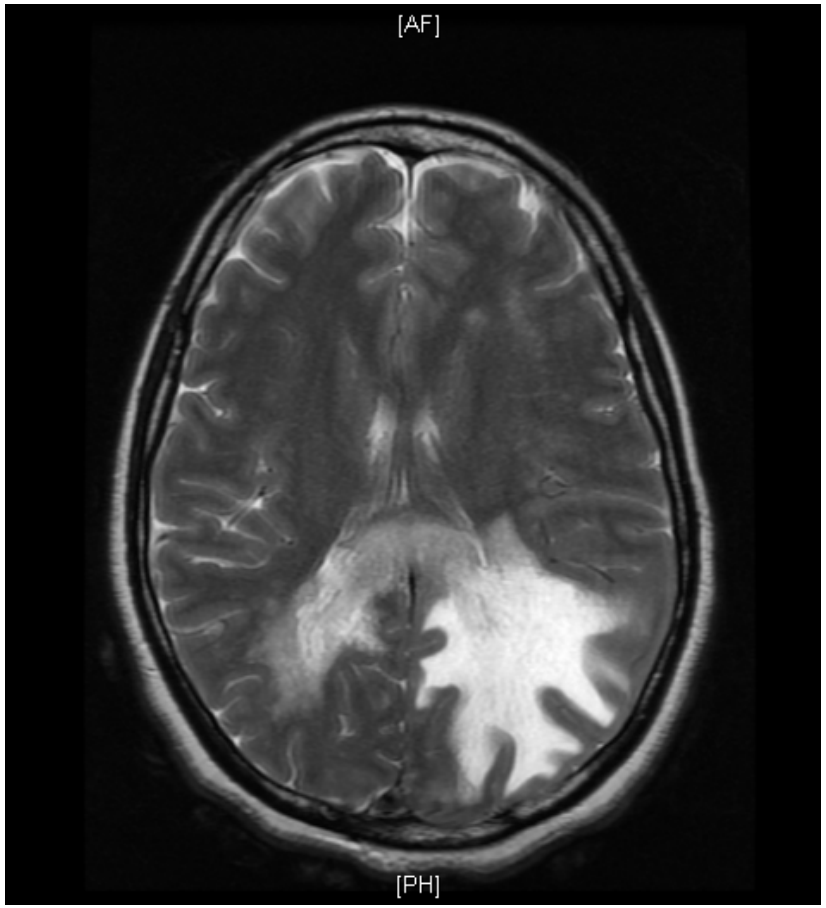


Case Presentation

- The patient continued to decline with the development of a dense R hemiparesis, dysarthria and confusion.
- CSF analysis was negative for all pathogens including JC virus and EBV.
- She was started on ART (Stribild) to treat HIV and PML and continued on anti-toxoplasma therapy.
- Because of continued decline on ART she received steroids (methylprednisolone for 3 days followed by an 11 day prednisone taper) with no effect.

Case Presentation

- Follow up imaging showed progression of L parietal lesion, now crossing the midline and with increased contrast enhancement
- Repeat CSF analysis remained negative for all pathogens



Case Presentation

- Brain biopsy performed: *Demyelination with viral cytopathic effect and immunoreactivity to SV-40 AB (a polyoma virus) confirming the diagnosis of PML.*
- Despite treatment with ART and mitrazapine the patient continued to decline. Her family decided to transition to comfort care and the patient died ~ 2 months into her illness.

Progressive Multifocal Leukoencephalopathy (PML)

PML

- The virus and genome
- Epidemiology and risk factors
- Pathogenesis
- Clinical presentation
- Diagnosis
- Treatment and Prognosis
- PML IRIS
- Other JC virus illnesses

PML: JC Virus

- Named for John Cunningham (first patient from whom the virus was identified). Virus identified in 1971
- A DNA polyomavirus : 5.13 Kb circular structure
  - Coding region (90% of the genome) for structural proteins
  - Regulatory region is highly variable and determines neurotropism
- Viral cycle
  - Asymptomatic primary infection in childhood
  - JC virus resides in kidney, bone marrow and lymphoid tissue of healthy individuals and can be detected (by PCR) in the urine of 1/3 of healthy people. Not typically found in blood

Tan and Koralnik Lancet Neurology 2010, Berger Neurology 2013

JC Virus: Epidemiology and Pathogenesis

- Sero-prevalence of JC virus
  - US: 39% (aged 24-30) and 65% (aged 65-74)
  - Finland: 72% in pregnant women aged 26-31
  - Switzerland: 68% of healthy blood donors aged 50-59
- Pathogenesis
  - Viral isolates from brains of patients with PML include mutations, deletions, duplications, insertions in the regulatory regions – likely responsible for enhanced replication
  - Leads to lytic infection of glial cells
  - An intact CTL response is necessary for control of JC virus and prevention of PML
  - Survivors of PML are those who eventually mount a CTL response – those without a CTL response most often die of the disease

Engels Int J Cancer 2005, Stolt, J Gen Virol 2003, Egli, J Infect Dis 2009

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PML: Epidemiology

- Before the HIV epidemic: a rare disease occurring in immunosuppressed patients with hematologic malignancies, transplant patients and those with chronic inflammatory disorders
  - Incidence rate of 4.4/100,000
- In the pre-ART HIV era – 5% of HIV infected patients developed PML!
- US study (1998-2005): 9675 cases
  - HIV 82% of cases
  - Hematologic cancers 8%
  - SOT 3%
  - Rhematologic disease < 1%
- New associations: Natalizumab for MS and Crohn's, Rituximab for SLE and Efalizumab for psoriasis

Molloy, Arthritis and Rheum 2009, Van Assche NEJM 2005, Langer-Gould NEJM 2005, Kleinschmidt-DeMasters NEJM 2005, Carson Blood 2005, Korman Arch Derm 2009

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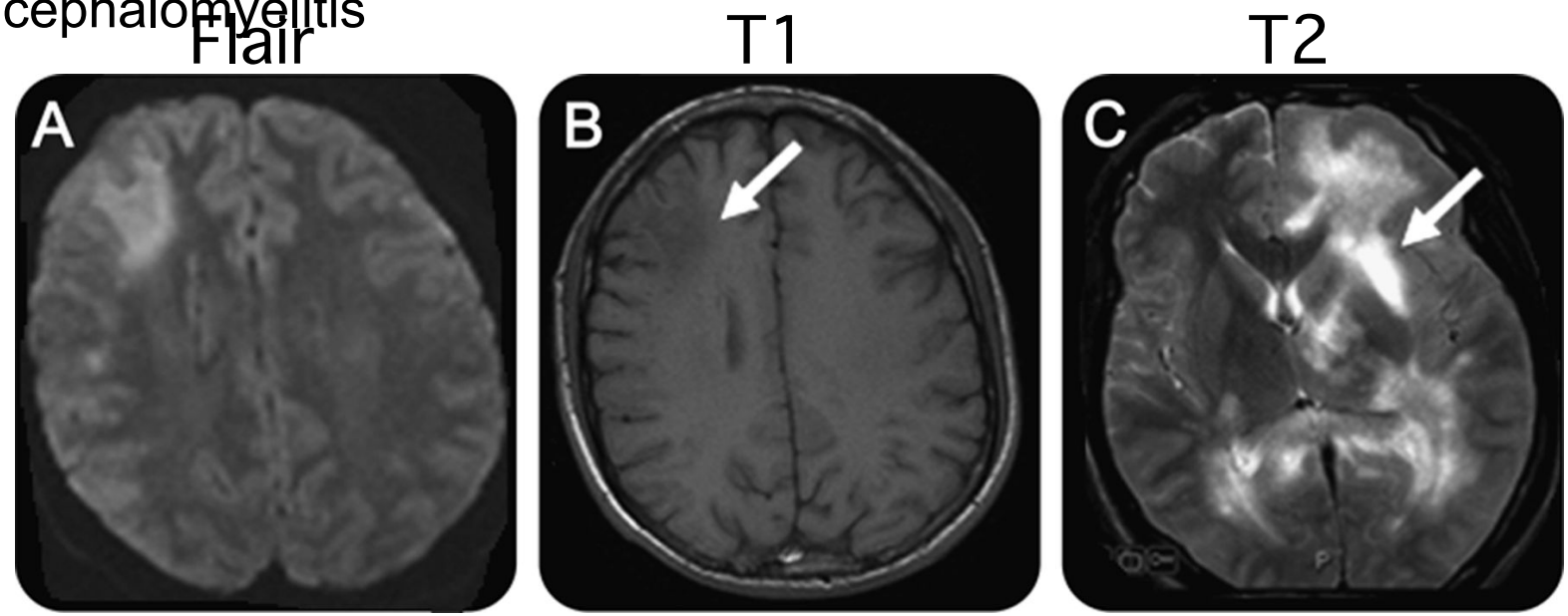
PML: Clinical Presentation

- Patchy demyelinization of the brain leading to:
  - Weakness, sensory deficits, hemianopsia, incoordination, aphasia
  - Seizures (16%)
  - Behavioral and cognitive dysfunction in 30 to 50%
- Optic nerves and spinal cord are usually spared

Tan Lancet Neurol 2010

PML: Radiographic Findings

- Patchy sub-cortical white matter disease – hyperintense on T2 weighted MRI
- Also may involve cerebellar peduncles, basal ganglia and thalamus
- Usually without enhancement or edema
- Differential: HIV, CMV, VZV, MS, CNS vasculitis, acute disseminated encephalomyelitis

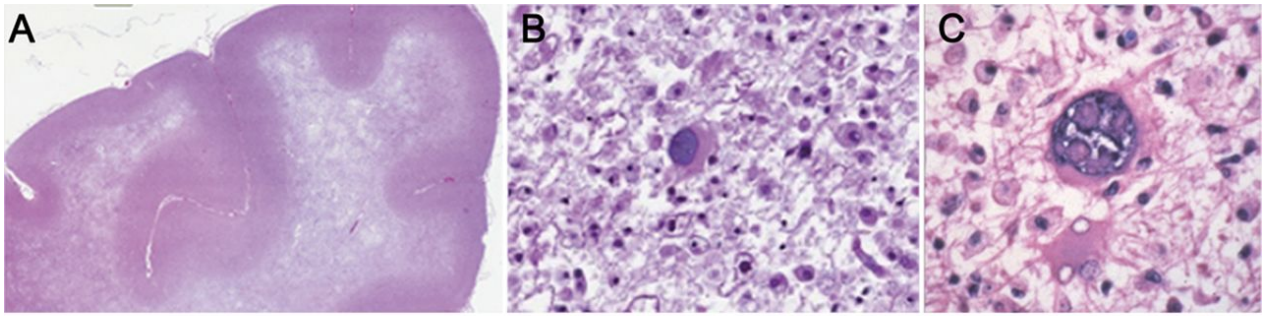


Berger Neurology 2013

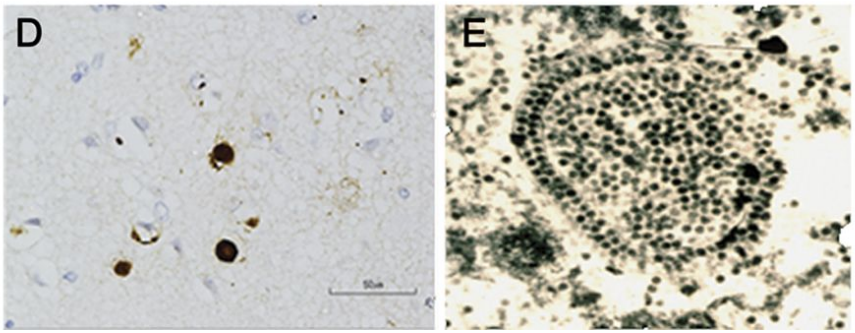
PML: Diagnosis

- Definitive diagnosis by brain biopsy demonstrating reactive gliosis, and the *classic triad* of bizarre astrocytes, large glial intranuclear inclusion and demyelinization and detection of JC virus proteins by in situ hybridization

Demyelinization Nuclear inclusion Bizarre astrocyte



In situ hybridization
For JCV proteins

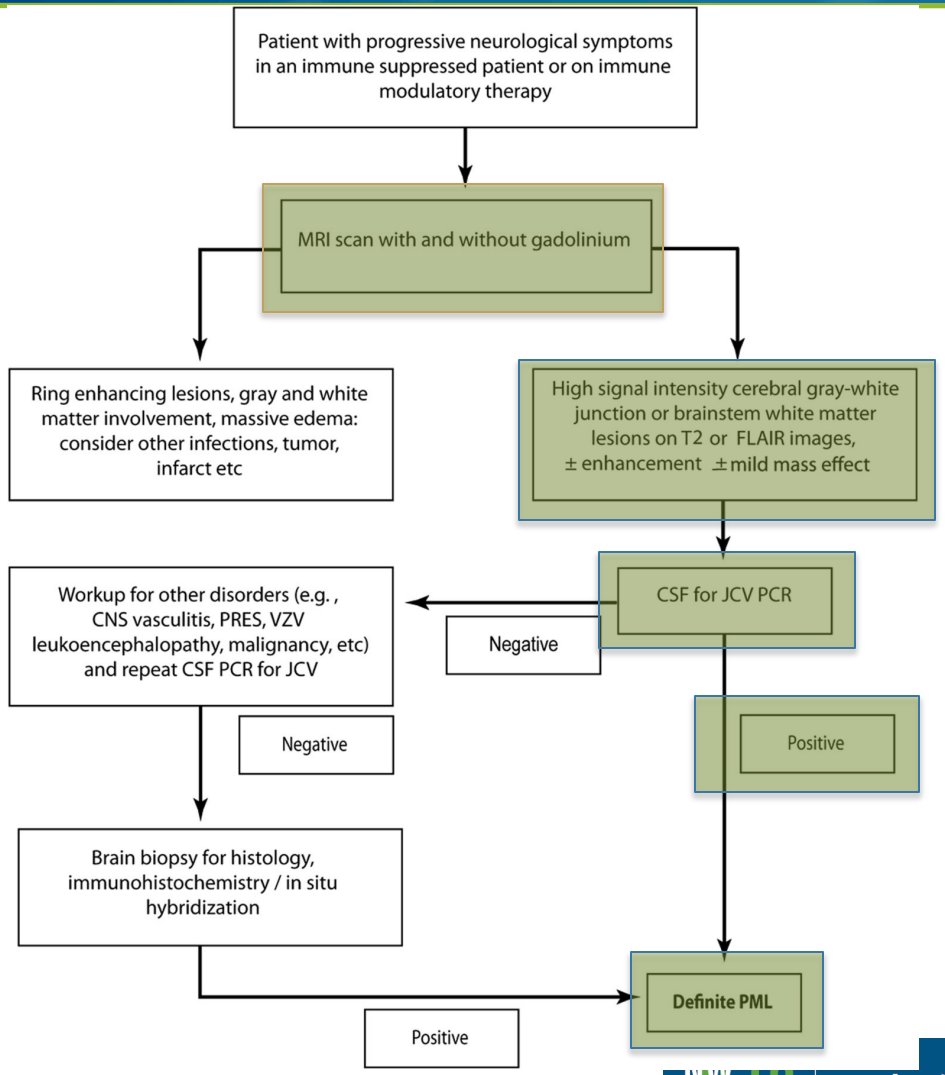


EM showing the virus

Berger Neurology 2013

PML: Diagnosis

- Without brain biopsy the diagnosis can be made based on a typical clinical presentation, radiographic appearance and the detection of JCV DNA in CSF
- CSF
  - WBC < 20
  - Elevated protein in 55%
  - JC virus by PCR: new ultrasensitive PCR > 95% sensitive. Lower sensitivity in those on ART with PML-IRIS. Rarely low copy numbers of JC virus can be detected in CSF of those without PML.



Berger Neurology 2013, Drews J Virol Methods 2000, Iacobaeus Mult Scler 2009

PML: Treatment

- No proven specific anti-viral therapy against JC virus exists
- Mirtazapine: binds to 5-HT2a, a cell receptor utilized by JC virus; 1 year survival of 62% Vs 45% in those not treated, N=25
- Mefloquine – works in vitro and currently in clinical trial

- Restore the immune system
  - HAART
  - Back off of immunosuppressive treatments whenever possible

Marzocchetti Neurology 2009, Tan Lancet Neurology 2010

PML: Prognosis and Outcome

- Factors associated with improved outcomes
  - Higher CD4 counts
  - Contrast enhancement on imaging studies
  - Low CSF JC virus: less than 50 – 100,000 copies
  - Detectable JC virus CTL
- Swiss cohort survival
  - Pre –HAART era 1 year mortality: 82.3%
  - Post – HAART era 1 year mortality 37.6%
- Outcome
  - 1/3 without disability
  - 2/3 with moderate to severe neurologic deficits

Tan Lancet Neurology 2010, Yiannoutsos, Ann Neurology 1999, Khanna CID 2009

PML: IRIS

- May be present in up to 23% of all cases of PML in HIV+ patients
- Clinically: After initiation of ART
  - Initial presentation of PML in patients with occult disease
  - Acceleration of symptoms in those with known PML
  - Time after HAART: 1-104 weeks
- Radiographically: Contrast enhancement and brain edema
- CSF: JC virus by PCR can be negative
- Histologically: demyelinated lesions infiltrated with lymphocytes
- Treatment options: anecdotal reports of improvement with
  - Holding HAART
  - Steroids

Tan, Lancet Neurology 2010, Tan Neurology 2009

Other JCV Diseases

- JC virus granule cell neuronopathy
  - Infection of the granule cell neurons of the cerebellum
  - Can occur with or without typical PML
  - Patients present with signs and symptoms of cerebellar dysfunction (ataxia and incoordination)
  - Diagnosis by biopsy
- JC virus encephalopathy
  - Case report of HIV negative woman with encephalopathy and seizures found to have JC virus infection of cortical neurons
- JC virus meningitis
  - Case reports of aseptic meningitis with JC virus in the CSF and without other detectable causes of meningitis

Tan Lancet Neurology 2010