MULTIFOCAL ENHANCEMENT IN FANCONI ANEMIA

A manifestation of IRIS and chronic polyoma virus infection?

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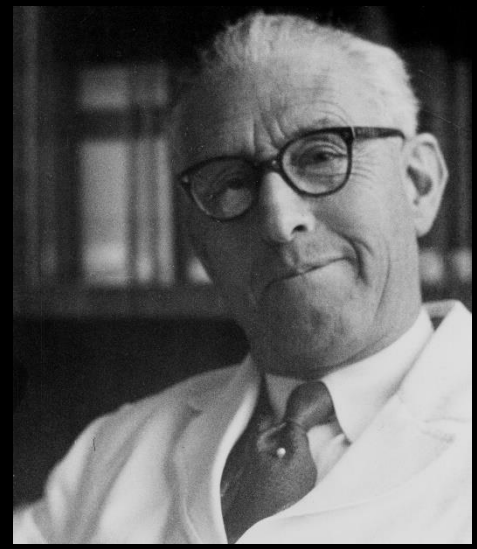
Fanconi Anemia



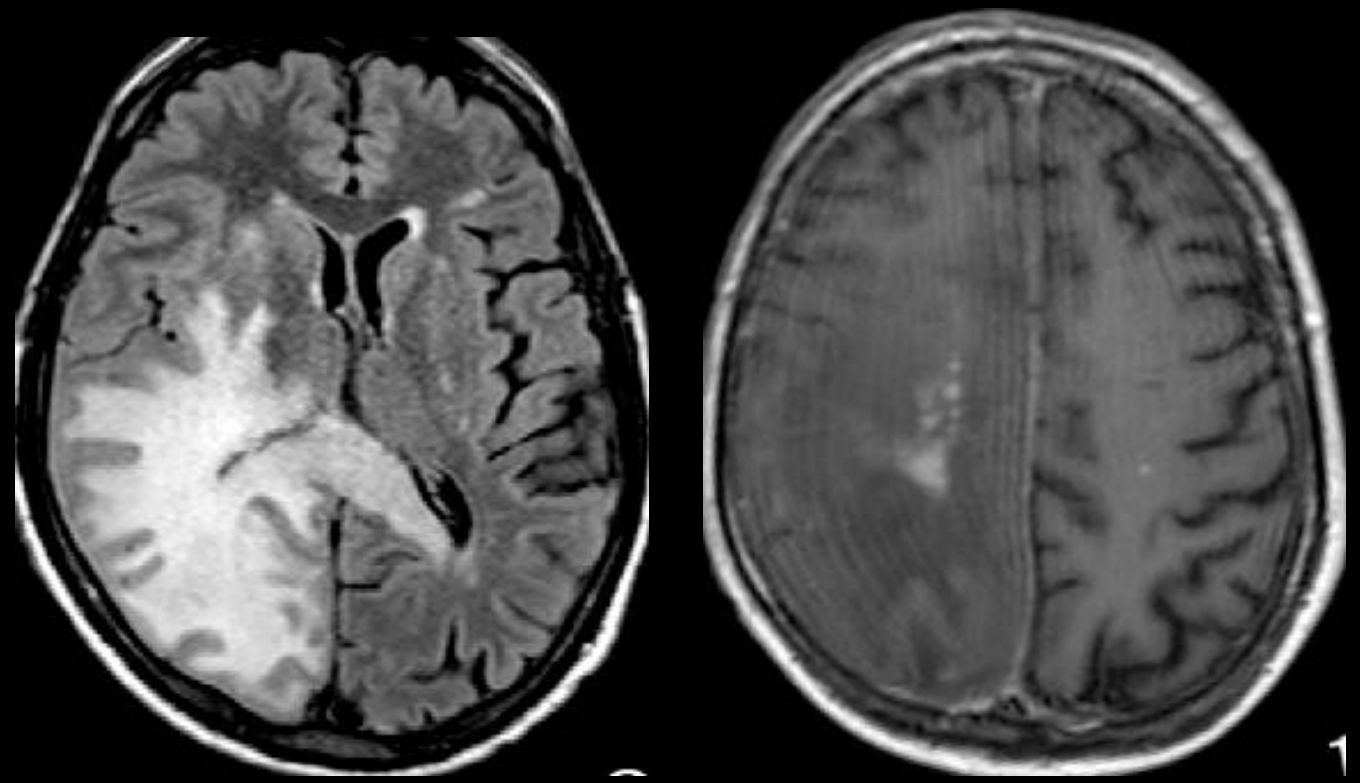
- Inherited bone marrow failure syndromes
  - Fanconi Anemia
  - Dyskeratosis congenita
  - Shwachman Diamond syndrome
  - Diamond-Blackfan anemia
  - Severe congenital neutropenia - Kostmann syndrome
  - Congenital amegakaryocytic thrombocytopenia
- Mutation in genes involved in DNA repair
- Increased risk of malignancy – viral associated
  - 1000x increased risk of HNSCC
    - 84% associated with HPV
- Immune dysfunction
  - Decrease in B and NK cells
  - Reduced function of cytoxic T cells and NK cells

Polyoma viruses

- 77 recognized polyoma virus species
- 13 are known to infect humans
- ~80% of the adult population is seropositive
- 2 known to cause pathology in immunocompromised
  - BK virus: hemorrhagic cystitis and nephropathy
    - exposure typically occurs by 3-4 years of age
  - JC virus: progressive multifocal leukoencephalopathy (PML)
    - exposure typically occurs by 10-14 years of age

Progressive multifocal leukoencephalopathy
PML

- Infection with JC virus
- Multifocal brain lesions in immunocompromised
  - T2/FLAIR abnl signal
  - Minimal enhancement
  - No calcification
- Progressive
  - 6 month avg survival after diagnosis
- No effective therapy in the face of a compromised immune system

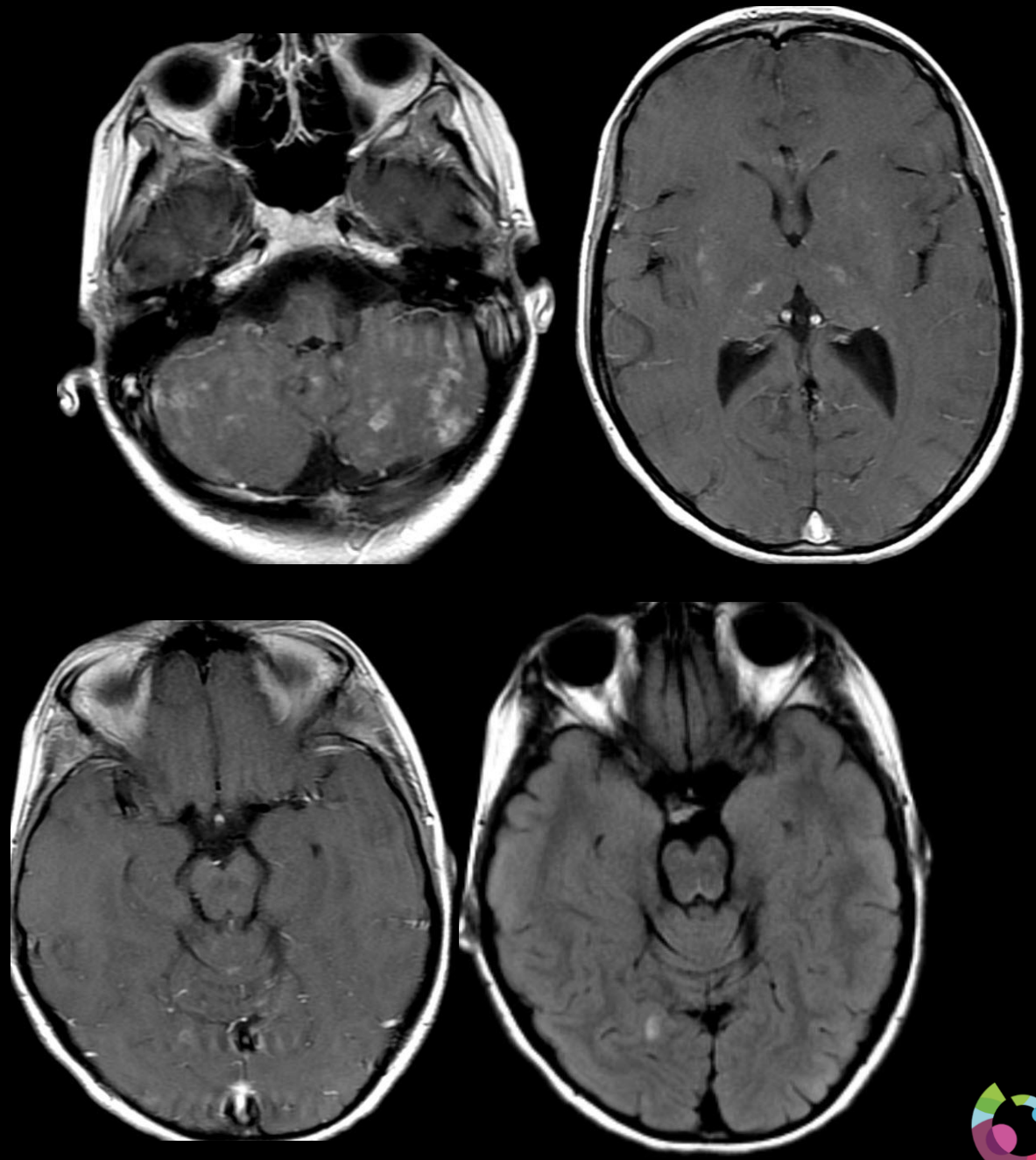


Immune Reconstitution Inflammatory Syndrome (IRIS)

- Clinical worsening of symptoms in patients with opportunistic infections due to recovery of the immune system
- Increased inflammatory (T cell) response with edema
  - HIV with PML
    - tx'd with HAART with recovery of immune fxn
    - Increased inflammation around PML
  - MS tx'd with natalizumab who develop PML
    - Increased inflammation with cessation of therapy and recovery of immune fxn
- Response to steroid therapy

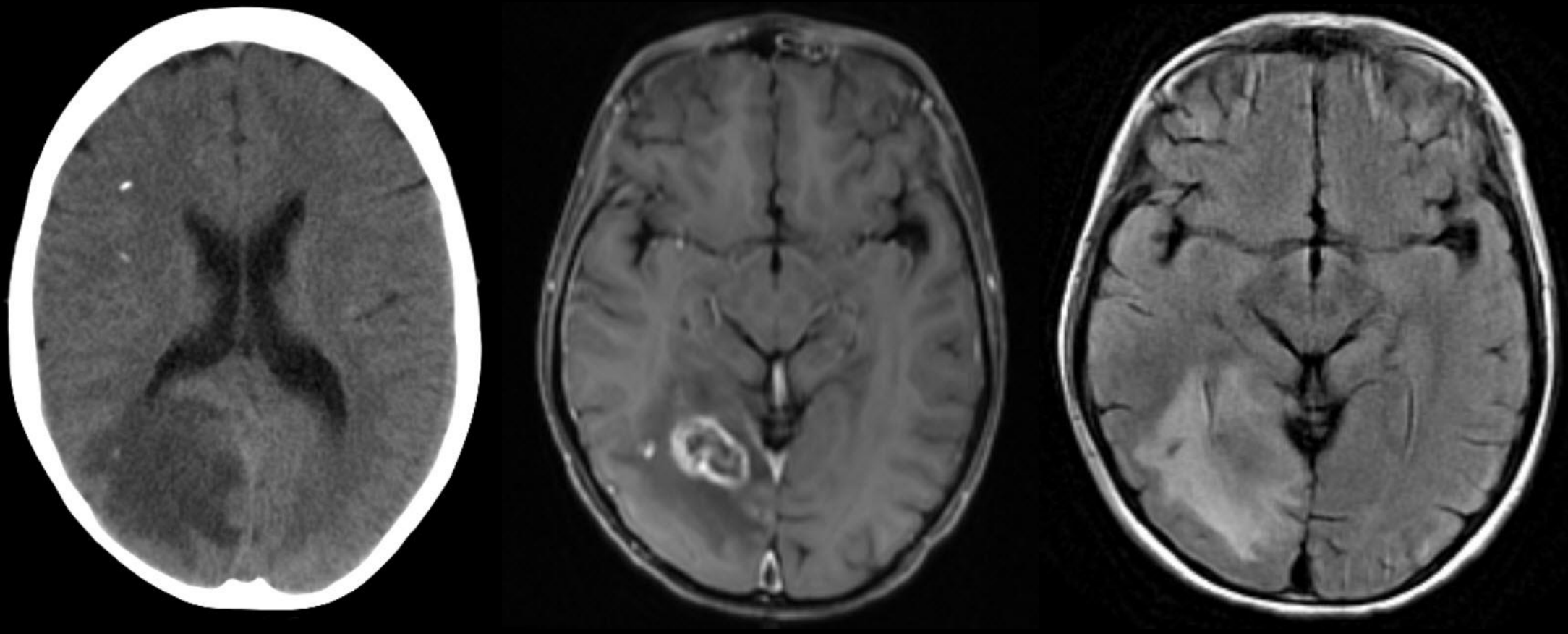
Case 1

- 20 yo ♀ with Fanconi anemia treated with BMT at age 10
- Presents to ED with numbness in her right arm, hip and tongue lasting for 20 minutes
- MR demonstrates multiple small enhancing foci throughout the brain, concentrated in the posterior fossa
- Declined further evaluation; discharged and lost to follow up



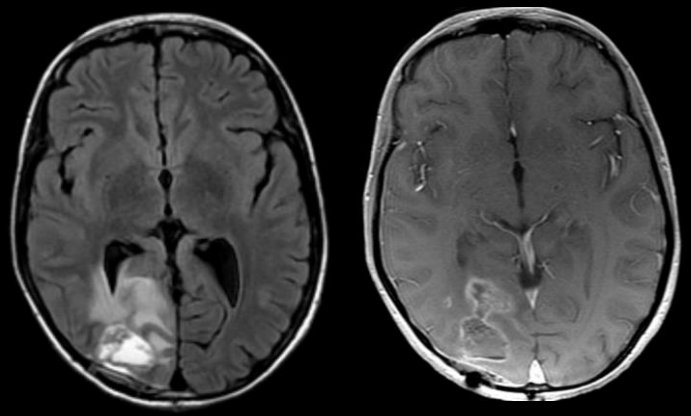
2 years later

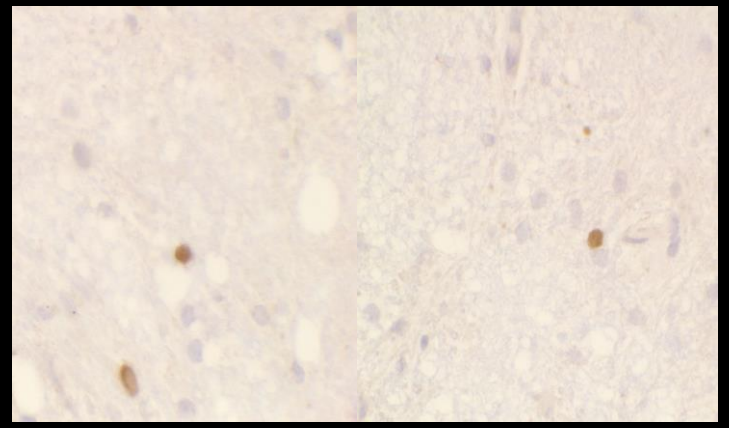
sudden onset of left sided hemianopsia

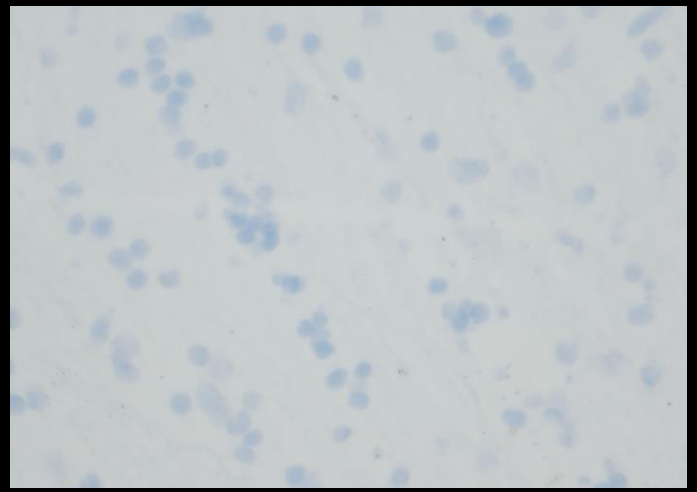


Surgical excisional biopsy

- Path
  - necroinflammatory process
  - necrosis, gliosis, scattered macrophages
  - negative for bacteria/fungus/EBV/CMV
- (+) for polyoma antigens*
  - Includes BK and JC virus
- (-) for BK virus**







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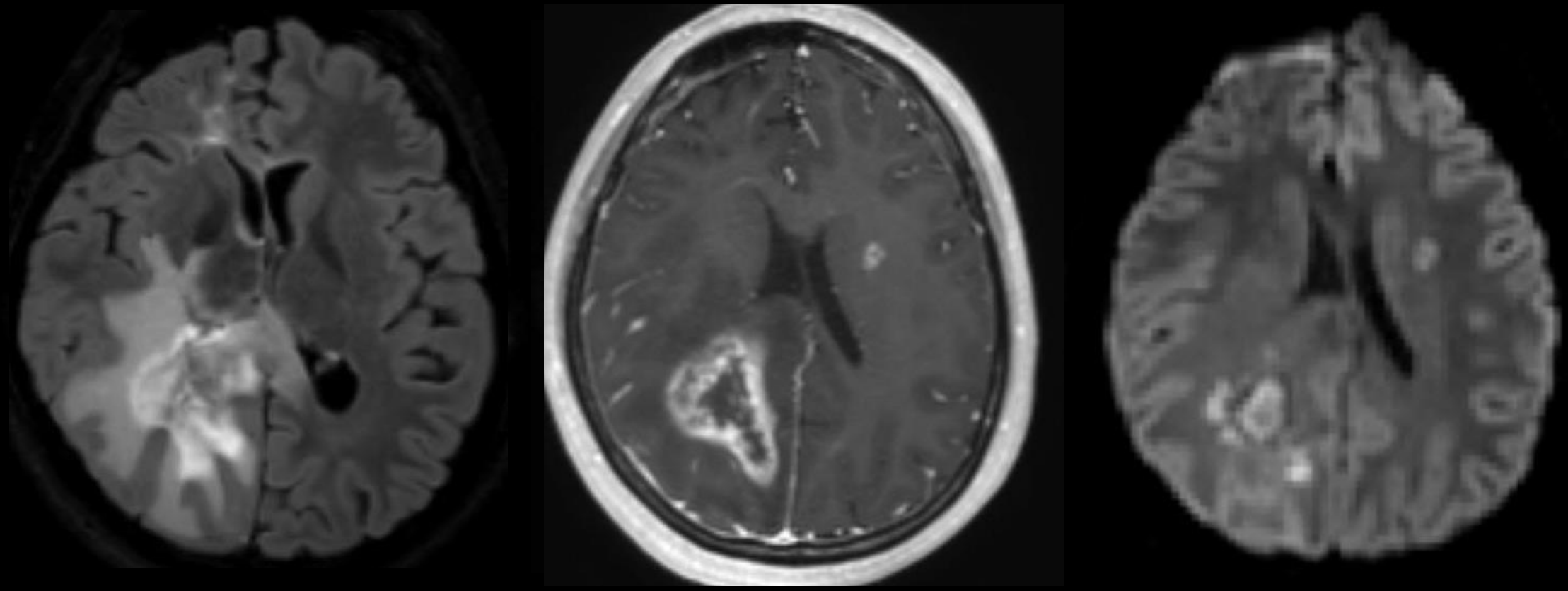
Case 2

- 20 yo ♂ with Fanconi anemia (no BMT) who developed transient L hemiplegia after a fall



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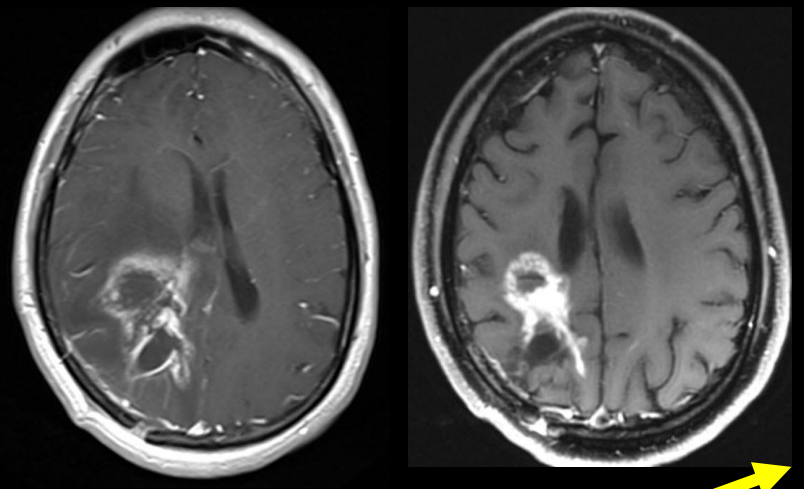

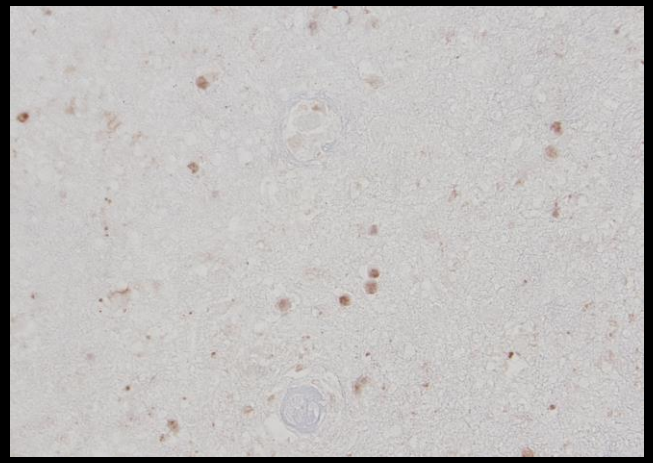

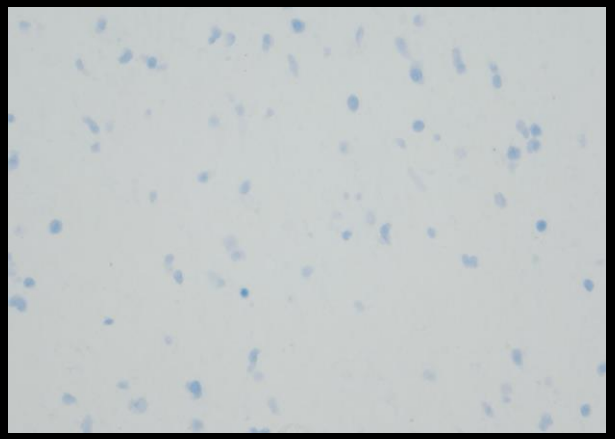

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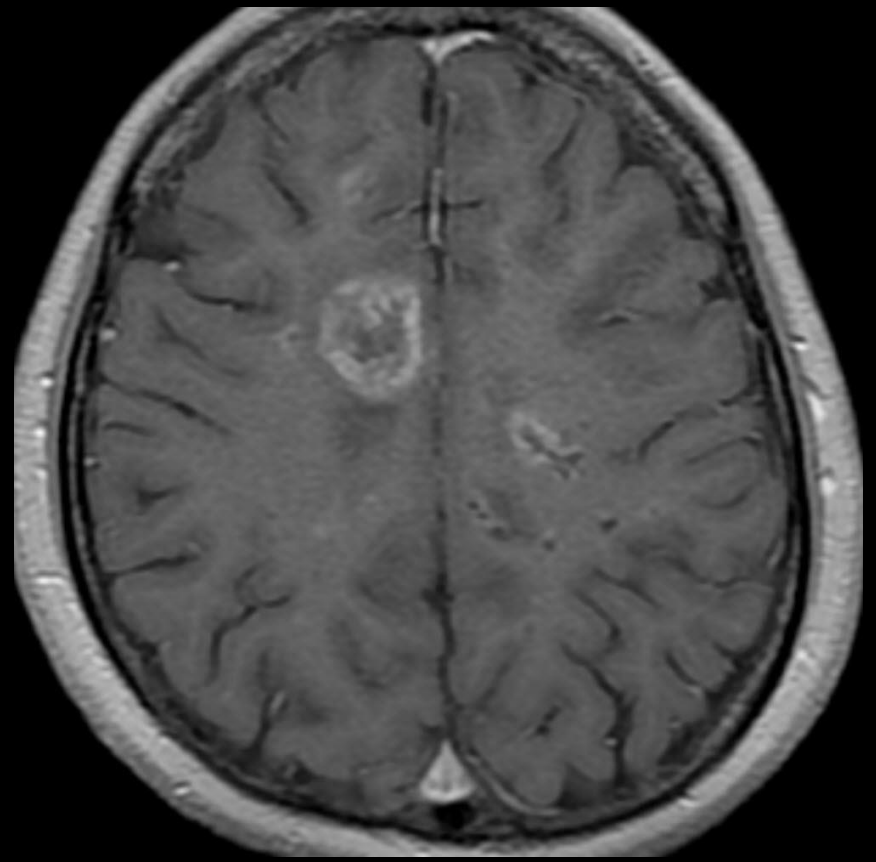
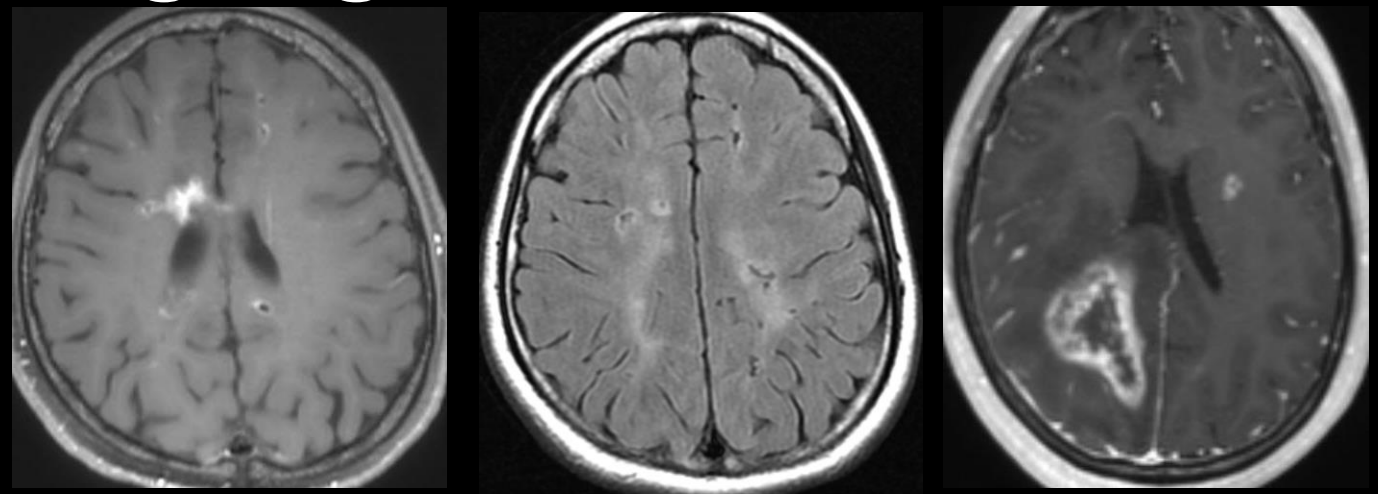
Database search

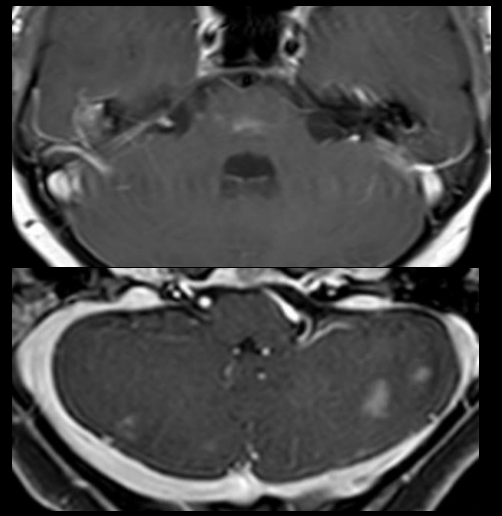
- MR/CT on 41 patients with FA
  - 8 with normal brain studies
  - 22 with other abnormalities
    - PRES, infarct
  - 5 with some similar findings, but other diagnoses
    - Toxo, CMV
  - 6 with characteristic imaging findings
    - 4 with serologic confirmation of JC exposure
      - 2 with biopsy confirmation
    - 2 of 6 not tested yet



Characteristic Imaging Features

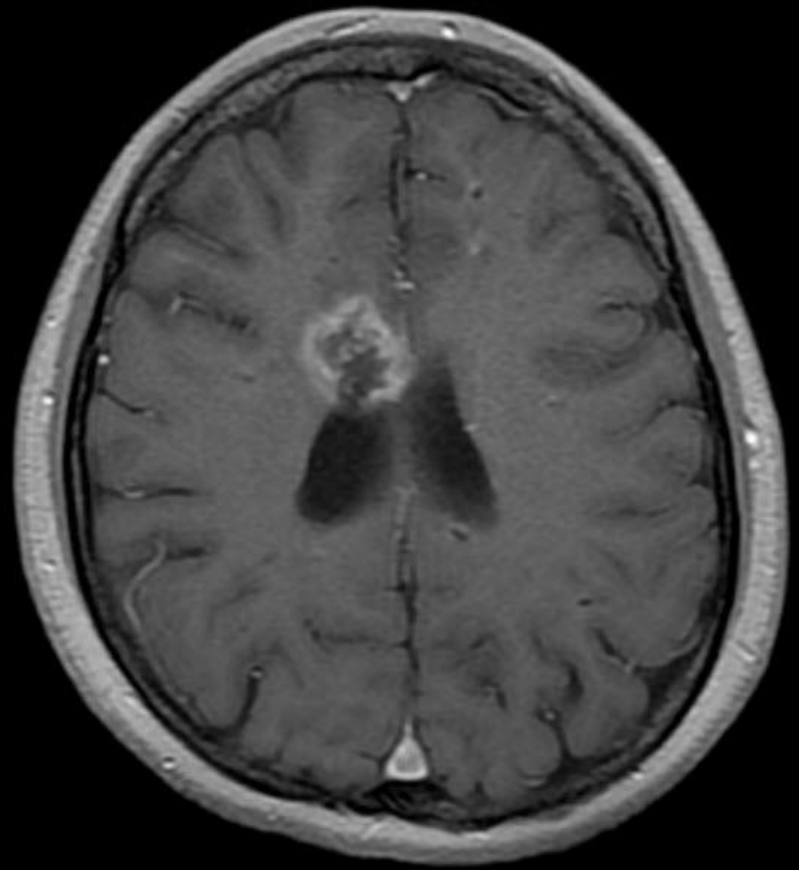
- Multiple small enhancing lesions
  - Ring enhancement
  - Little or no surrounding edema
  - Frequent cerebellar and brainstem involvement (6/6)
- Calcifications
  - Associated with many (but not all) enhancing lesions (6/6)
- Dominant mass with edema (3/6)
- 2 patients had spine imaging
  - Waxing and waning cord lesions





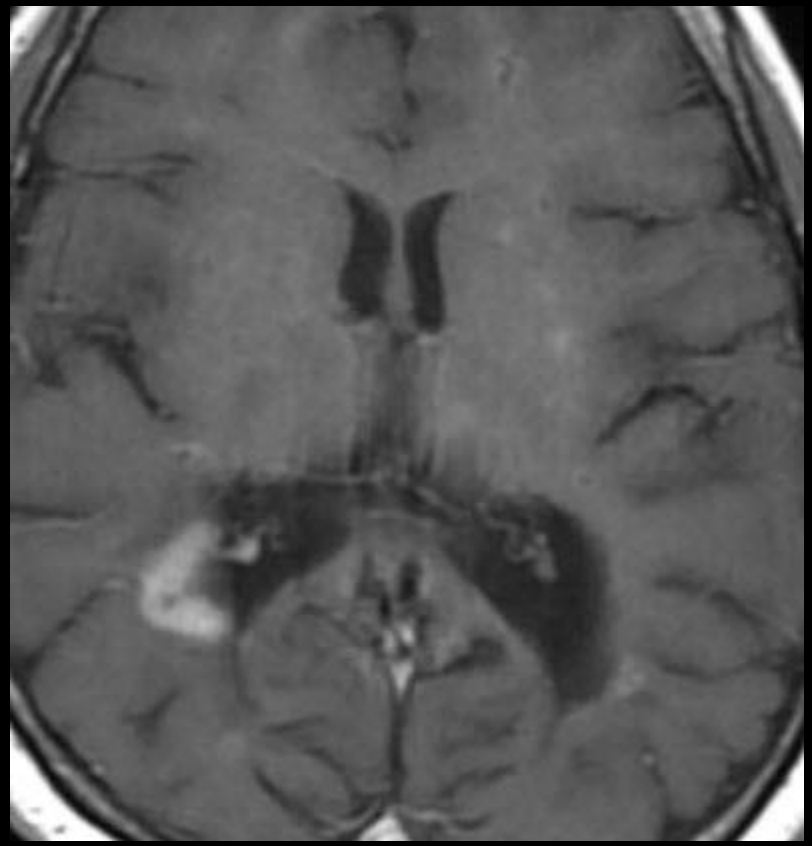
Summary of observations

- 6/41 (15%) FA patients have an unusual pattern of calcifying and enhancing brain lesions
  - 2 with spine imaging also have subtle spinal cord lesions
- 3 have developed mass-like lesions with necrosis
  - Biopsies in 2 have confirmed presence of JC virus in lesions
- Enhancement and edema respond to steroid therapy



Conclusions - Hypothesis

- Increased longevity = more FA patients with JC infection
- JC infection is pathologic in FA
  - Multifocal inflammatory lesions
  - ~~Immune system dysfunction?~~
  - Hampered DNA repair
- BMT normalizes immune system function
  - DNA repair in brain cells is still hampered
    - Viral infection remains pathologic
  - May cause IRIS in response to these lesions
  - Necrotic mass lesion – not PML
    - Responsive to steroid therapy



Conclusions

- FA patients are uniquely susceptible to JC virus infection
  - Because of DNA repair defects
- FA patients should be monitored for JC infection with brain MR imaging
  - Small enhancing lesions with Ca++
  - Posterior fossa, spinal cord
- Restoration of immune function with BMT does not decrease risk
  - May cause IRIS with large necrotic lesions