Inflammatory and Infectious Diseases of the CNS

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Objectives

- Understand the history, imaging, and classic histopathology of demyelinating diseases
  - Multiple Sclerosis
  - Progressive Multifocal Leukoencephalopathy
- Understand the usual clinical history and basic histopathologic work-up of CNS infections:
  - Bacterial
  - Fungal
  - Parasitic CNS infections

Myelin Pathologies

Demyelinating

- Immune-mediated destruction of biochemically normal myelin
- Multiple sclerosis, PML, acute disseminated encephalomyelitis

Dysmyelinating (leukodystrophies)

- Inherited destruction of chemically (i.e. genetically) abnormal myelin
- May involve both central and peripheral myelin
- Metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy

Hypomyelinating

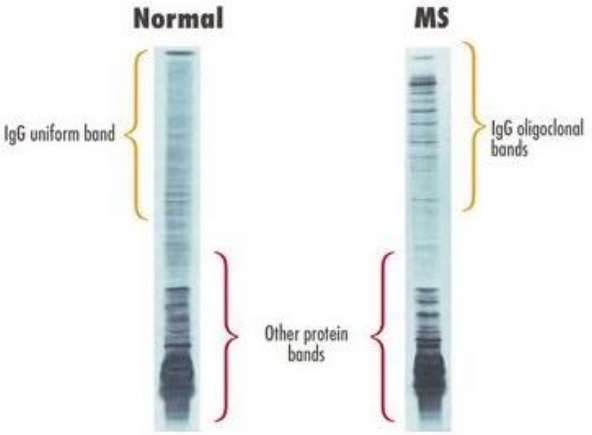
- Paucity of biochemically normal myelin deposition during development
- Alexander's disease, vanishing white matter disease

Myelinolytic

- Intramyelinic edema of biochemically normal myelin
- Central pontine myelinolysis, vitamin B12 deficiency, toxins

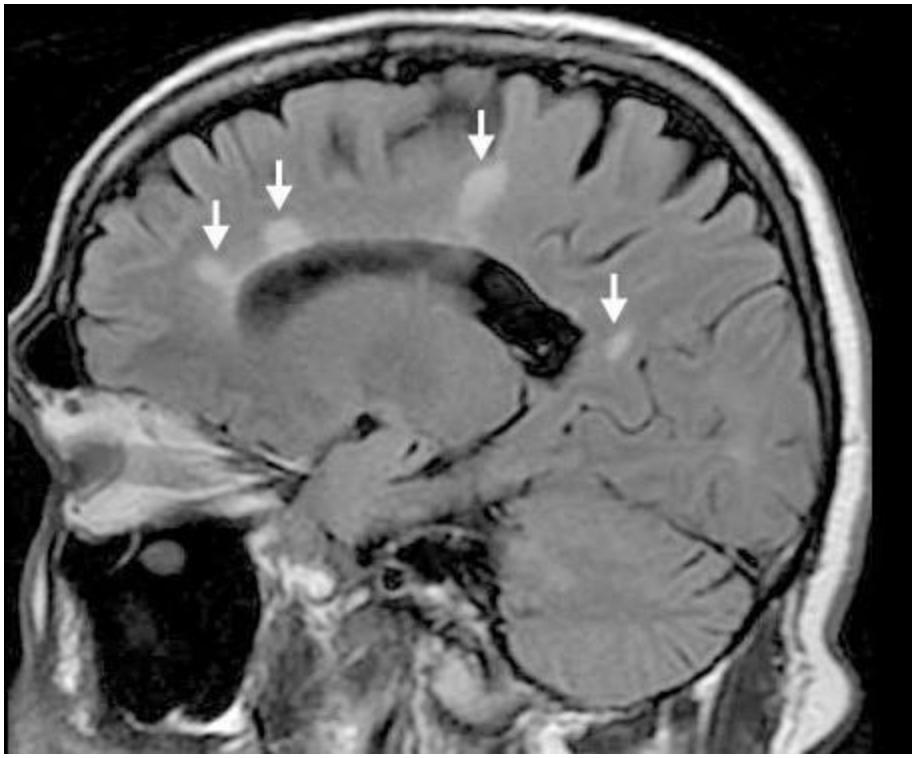
Multiple Sclerosis

- Inflammatory, sporadic destruction of biochemically normal myelin by the immune system
- Clinical history:
  - Young women, often with vision problems
  - Neurologic symptoms related to the location of the lesion
  - Typically NOT diagnosed histologically
    - Two lesions separated in time and space (and typically, symptoms)
    - CSF Protein Electrophoresis shows oligoclonal bands



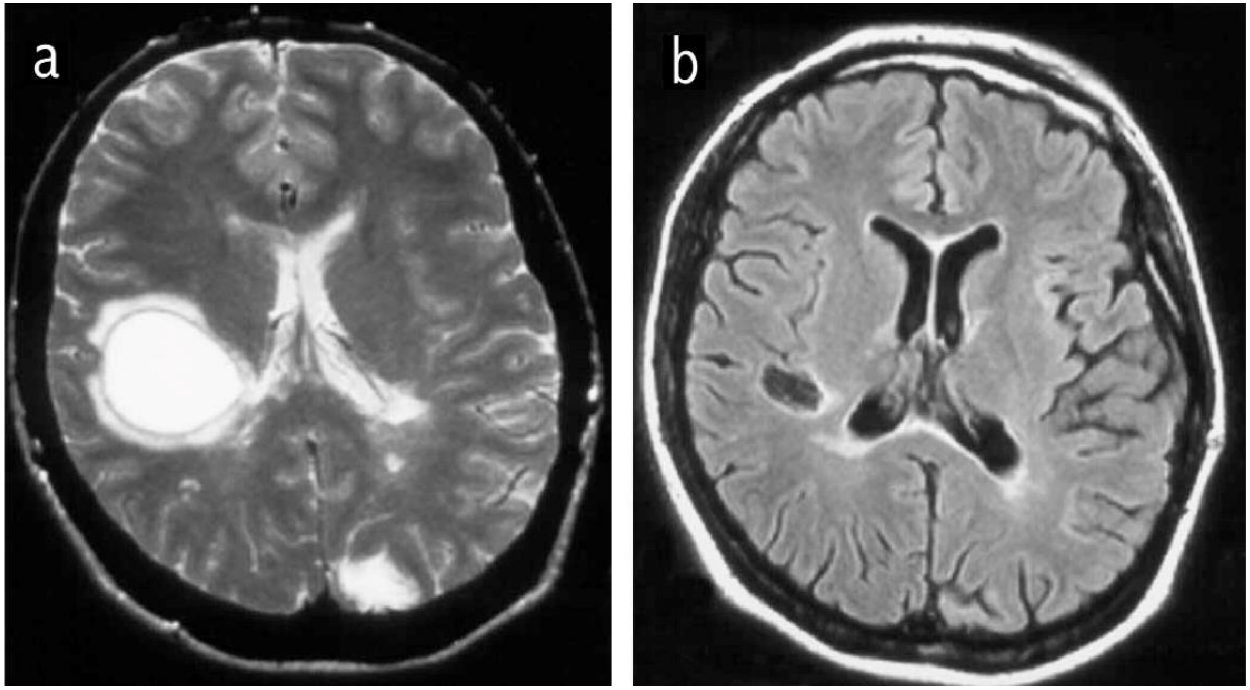
From “multiple-sclerosis-research.org”

MS- MRI (classic)
“Dawson’s Fingers”



From “mayoclinic.org/diseases-conditions/multiple-sclerosis/multimedia/multiple-sclerosis-mri-scan”

MS- MRI (mimicking tumor)



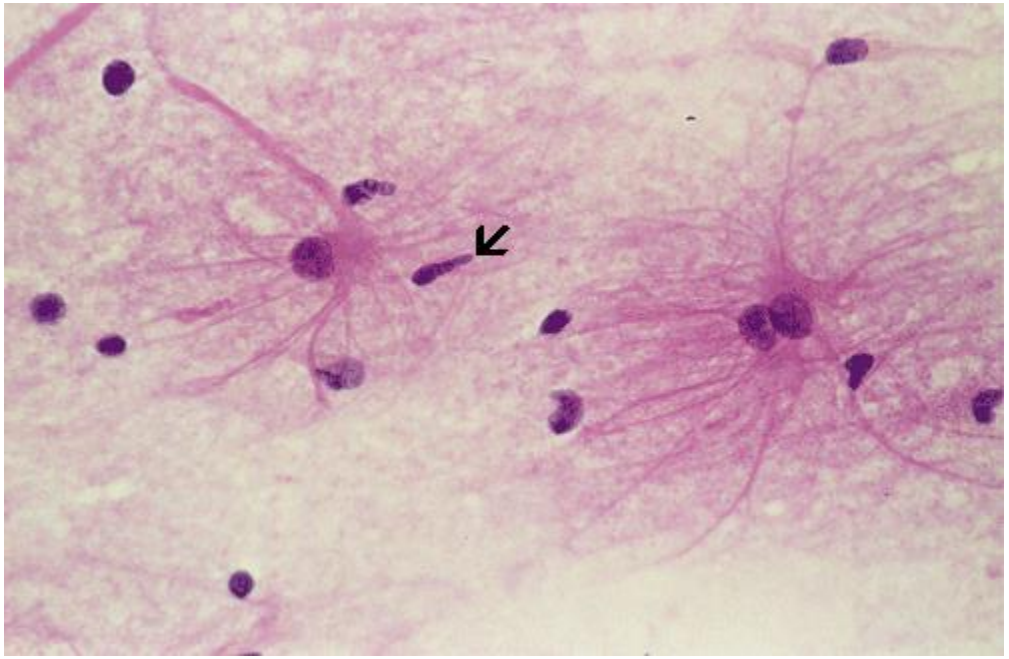
Capello et. al. Tumor like multiple sclerosis lesions: neuropathological clues. Neurol Sci. 2001 Nov.

Multiple Sclerosis

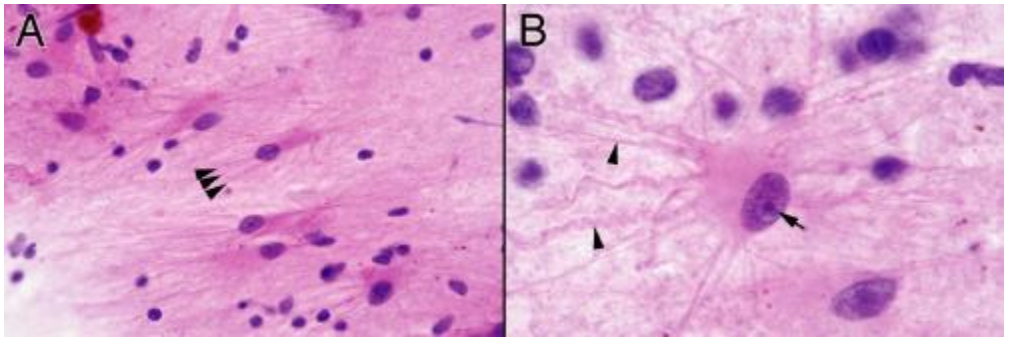
- Cellular components:
- Reactive astrocytes
- Lymphocytes
  - Predominantly T-cells
  - Often perivascular
- Foamy macrophages

Reactive astrocytes

Smear: Abundant eosinophilic cytoplasm, numerous processes

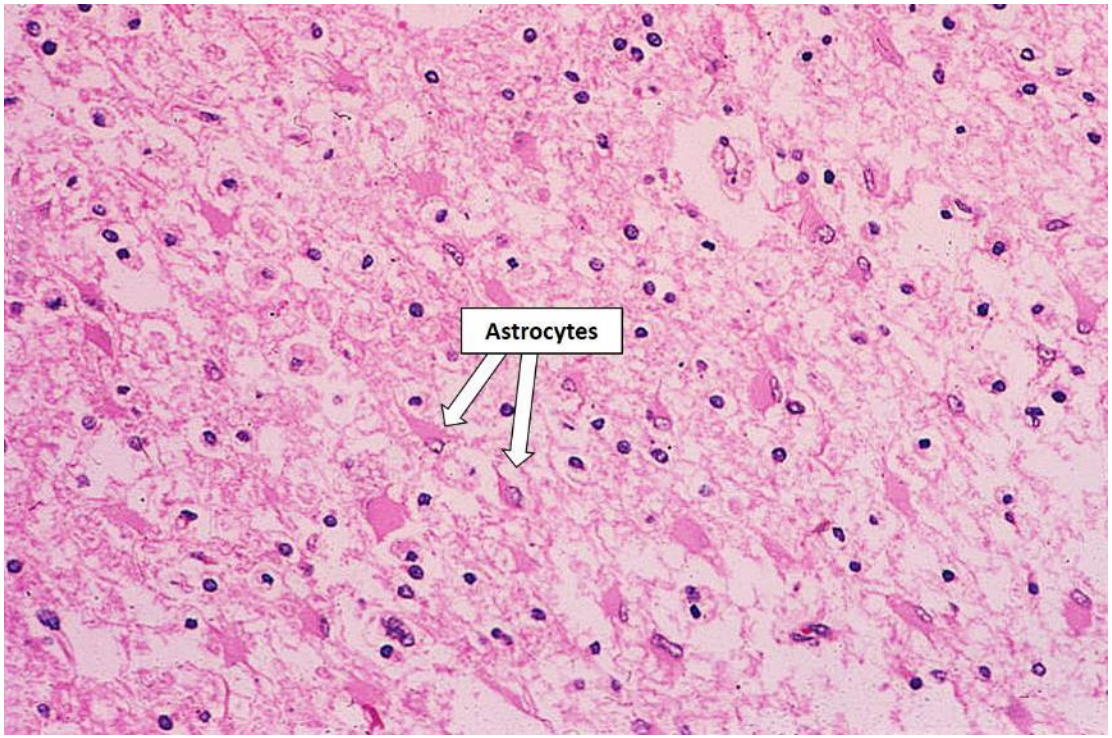


Sentinels/squiddies, from ‘The Matrix’



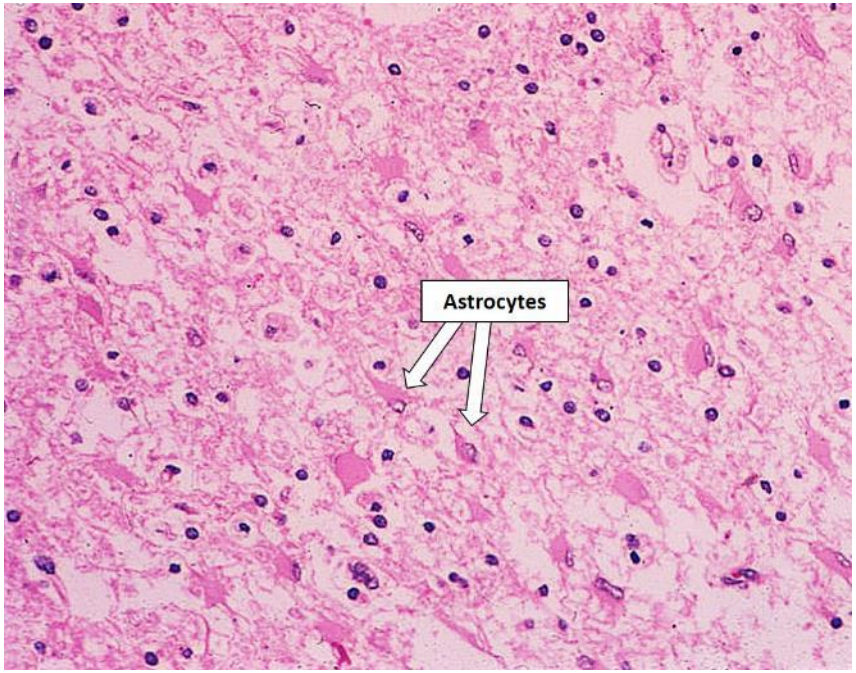
Reactive astrocytes

Frozen: eosinophilic cytoplasm, evenly spread out

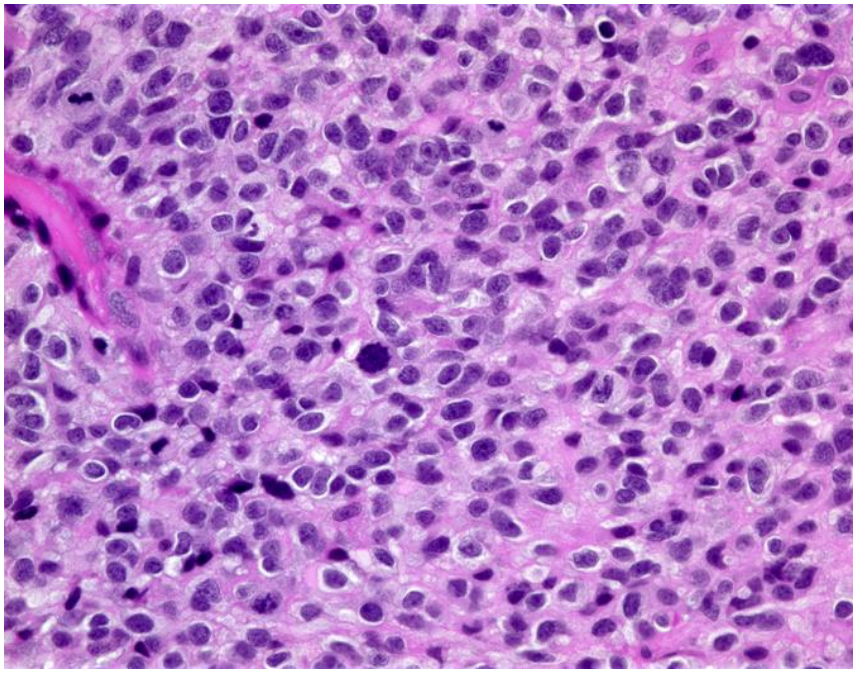


Astrocytes: Reactive vs neoplastic

Reactive

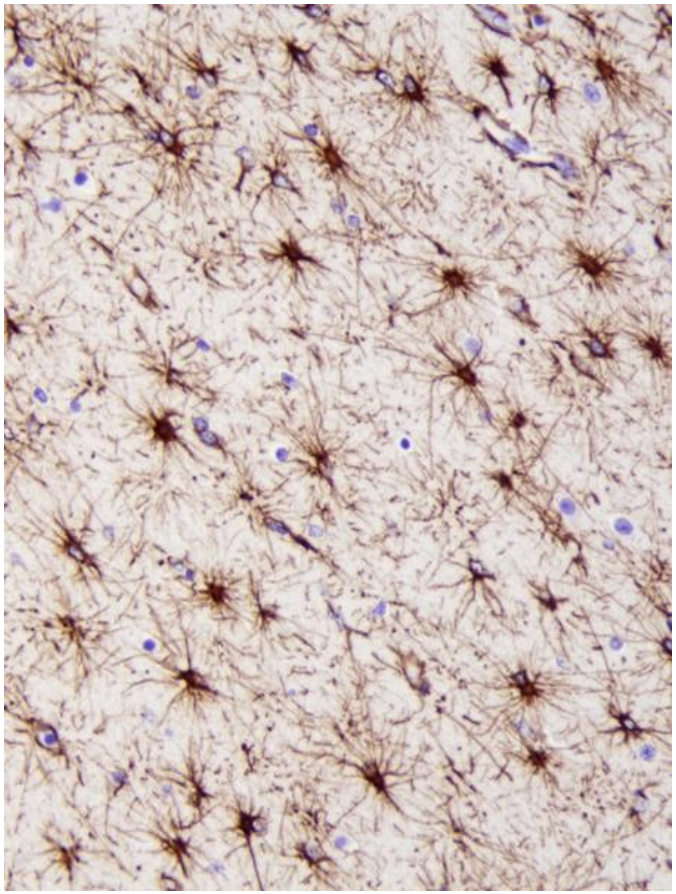


Grade III Astrocytoma

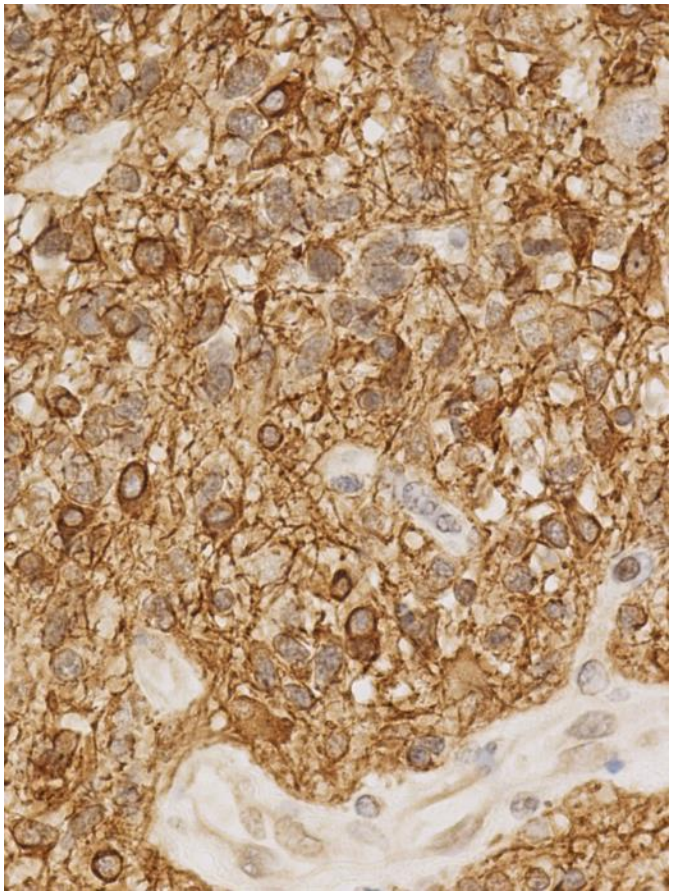


Astrocytes: Reactive vs neoplastic

Reactive astrocytes



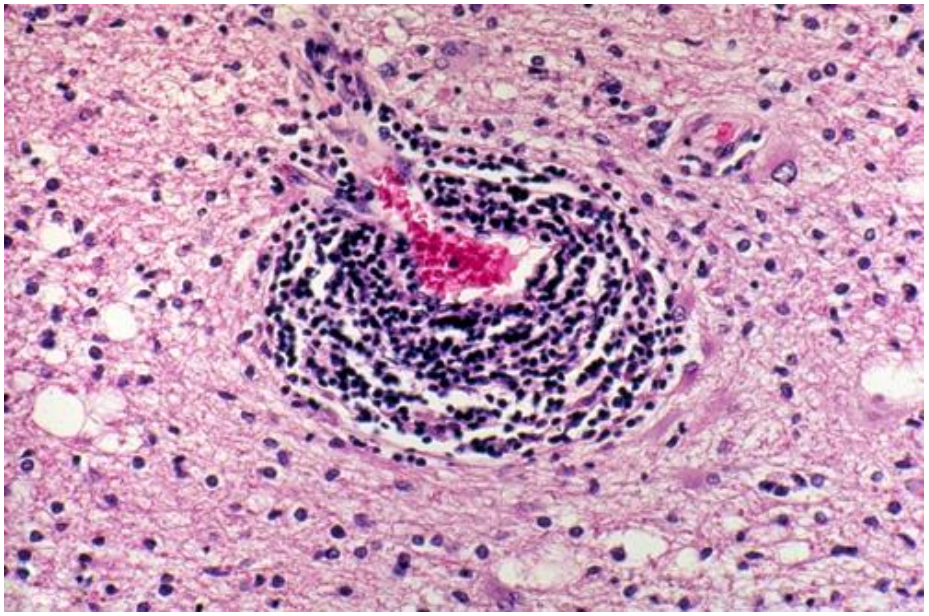
Astrocytoma



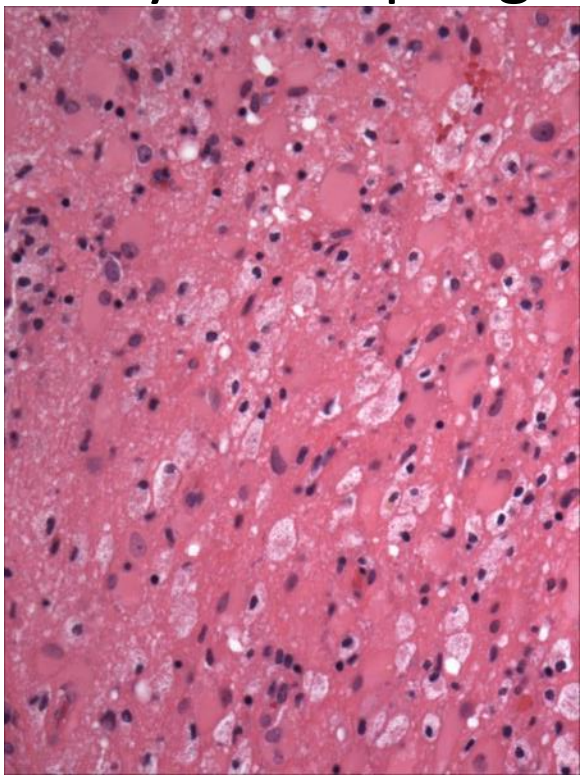
GFAP Immunohistochemistry

Demyelination

Perivascular lymphocytes



Foamy macrophages



Demyelination Suspected on FS: What to report…

- "Inflammatory lesion present, macrophages and lymphocytes suggest demyelination; *recommend flow cytometry AND broad microbial cultures*"
- NOT….
  - "Demyelination, c/w multiple sclerosis"
  - "Favor MS"

Demyelination:

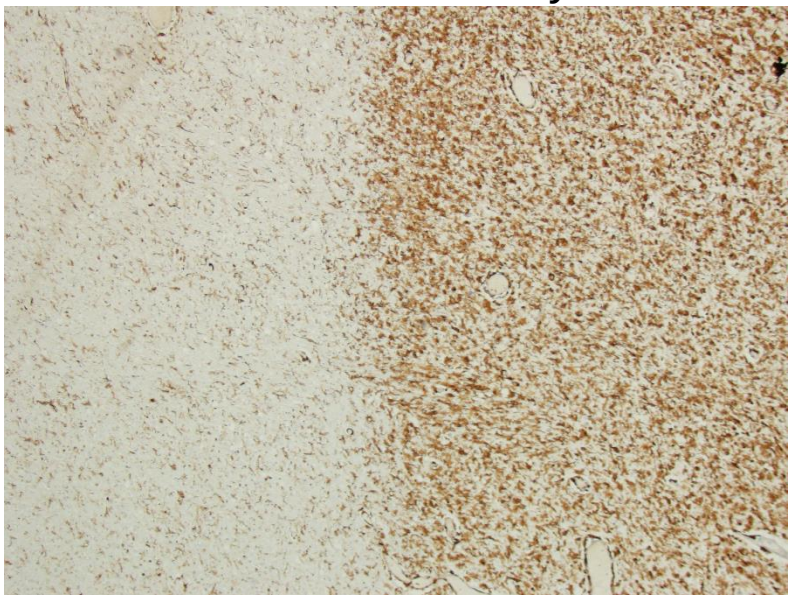
Work-up of permanent sections……

MS Plaques

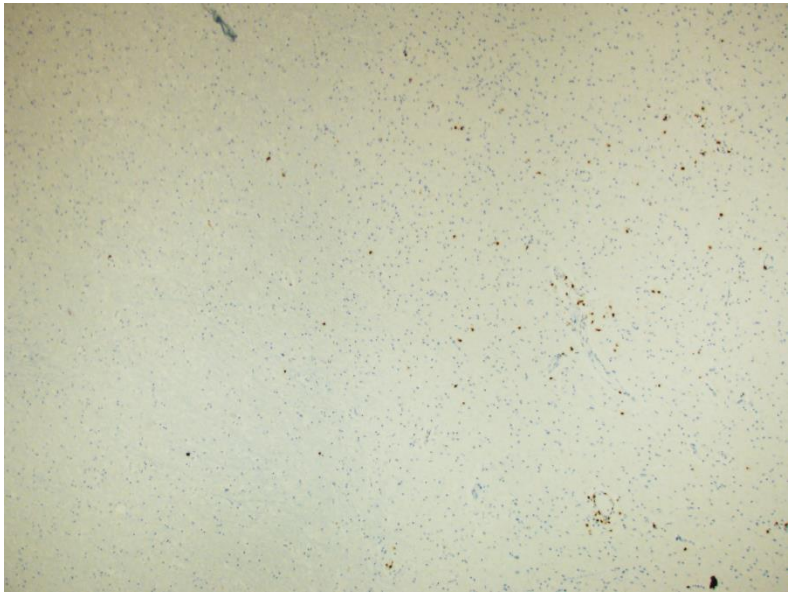
B/L foci of MCP demyelination

Normal Demyelinated

Macrophages
(highlighted by CD163 IHC)



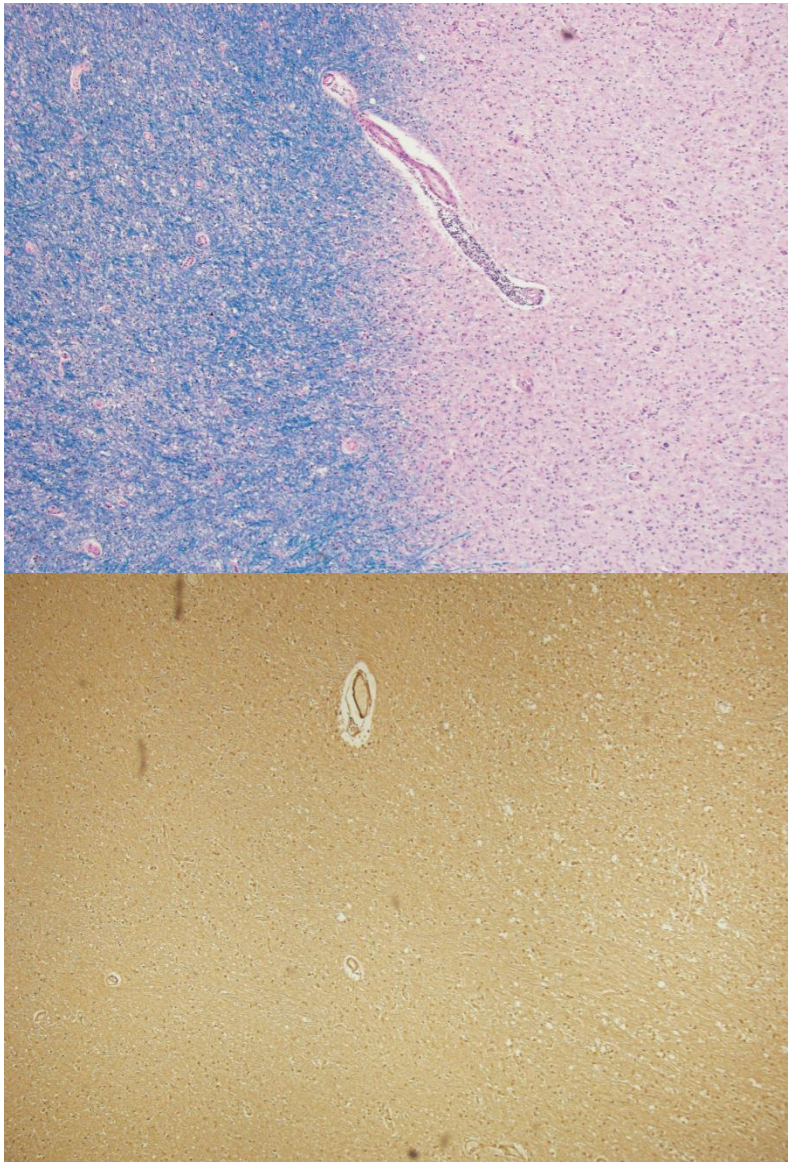
T-cells
(highlighted by CD3 IHC)



Normal Demyelinated

Loss of myelin (LFB)

Sparing of axons (Neurofilament IHC stain for axons)



Immunocompromised states

- HIV/AIDS
- Iatrogenic
  - Steroids
  - Antibodies (anti-TNF-α or anti-α4 integrin)
  - Transplant
  - Chemotherapy
- Marrow suppressive disease
  - Leukemia
  - MDS
  - Aplastic anemia
- Congenital
  - CVID
- Others

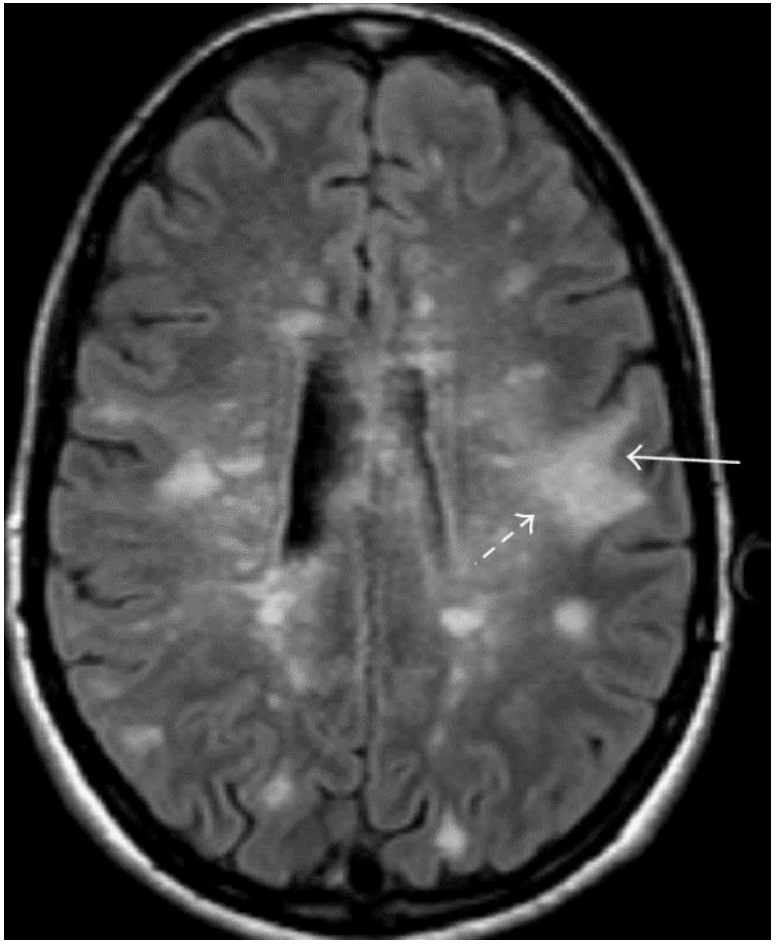
ALWAYS CULTURE!!!!

Progressive Multifocal Leukoencephalopathy (PML)

- First suggested to be an opportunistic infection by EP Richardson in 1961
- Caused by JC virus
- Polyomavirus (others are SV40 and BK)
  - dsDNA virus
  - Binds to sialic acid residues on the cell surface
- 75-80% of all adults infected (serology)
- Usually diagnosed clinically
- Symptoms:
  - mild change in mental status, progressing to encephalopathic symptoms
- Histo: foamy macrophages and bizarre oligodendroglial cells

PML: Imaging

- FLAIR shows
  - Sharp border beneath the subcortical U-fibers (arrow)
  - Hazy, ill-defined medial border (dashed arrow)

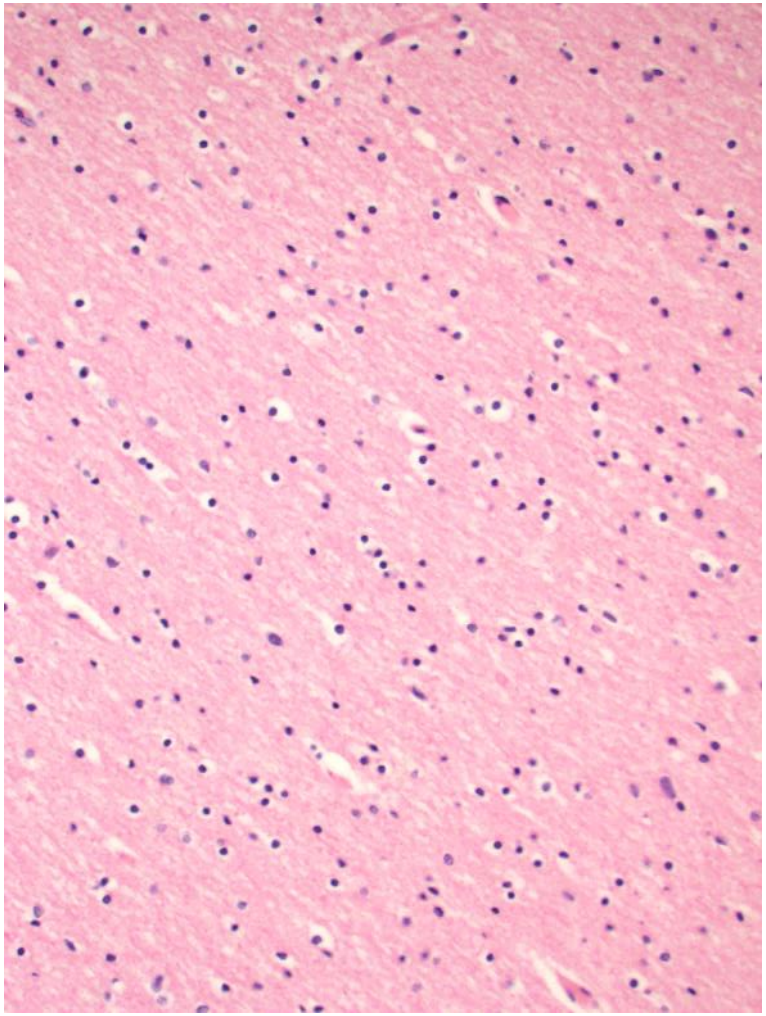


From “Honce JM et. al. Neuroimaging of Natalizumab Complications in Multiple Sclerosis: PML and Other Associated Entities. Multiple Sclerosis International. 20 Sept. 2015.”

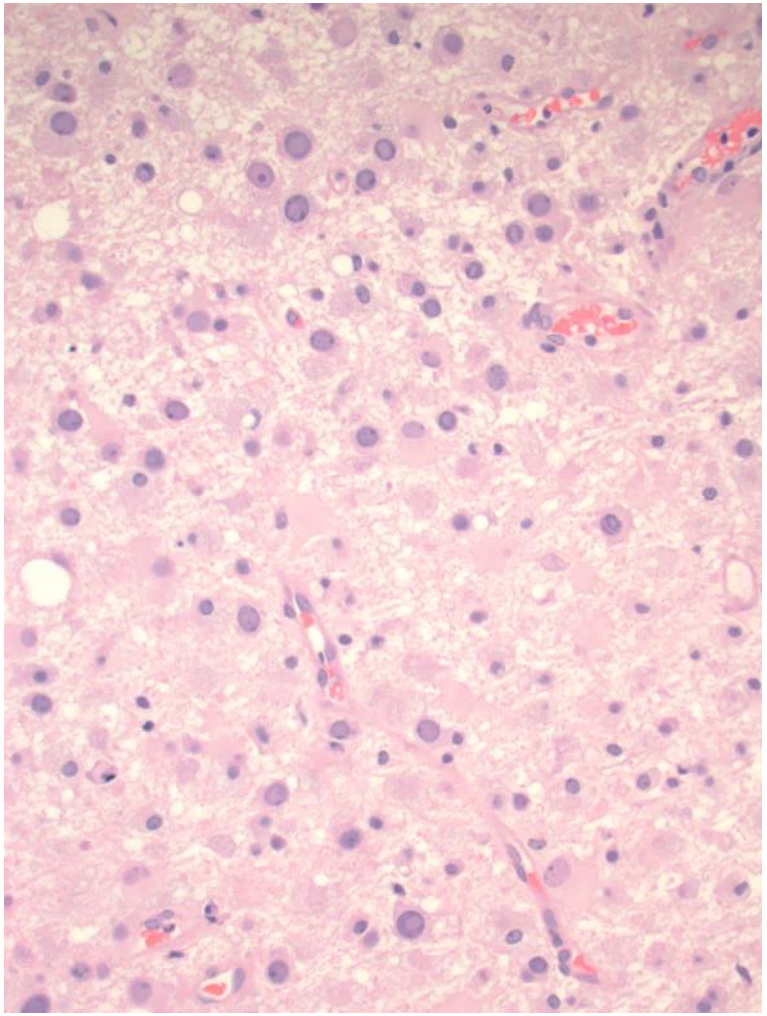
PML

Histology

Normal White Matter

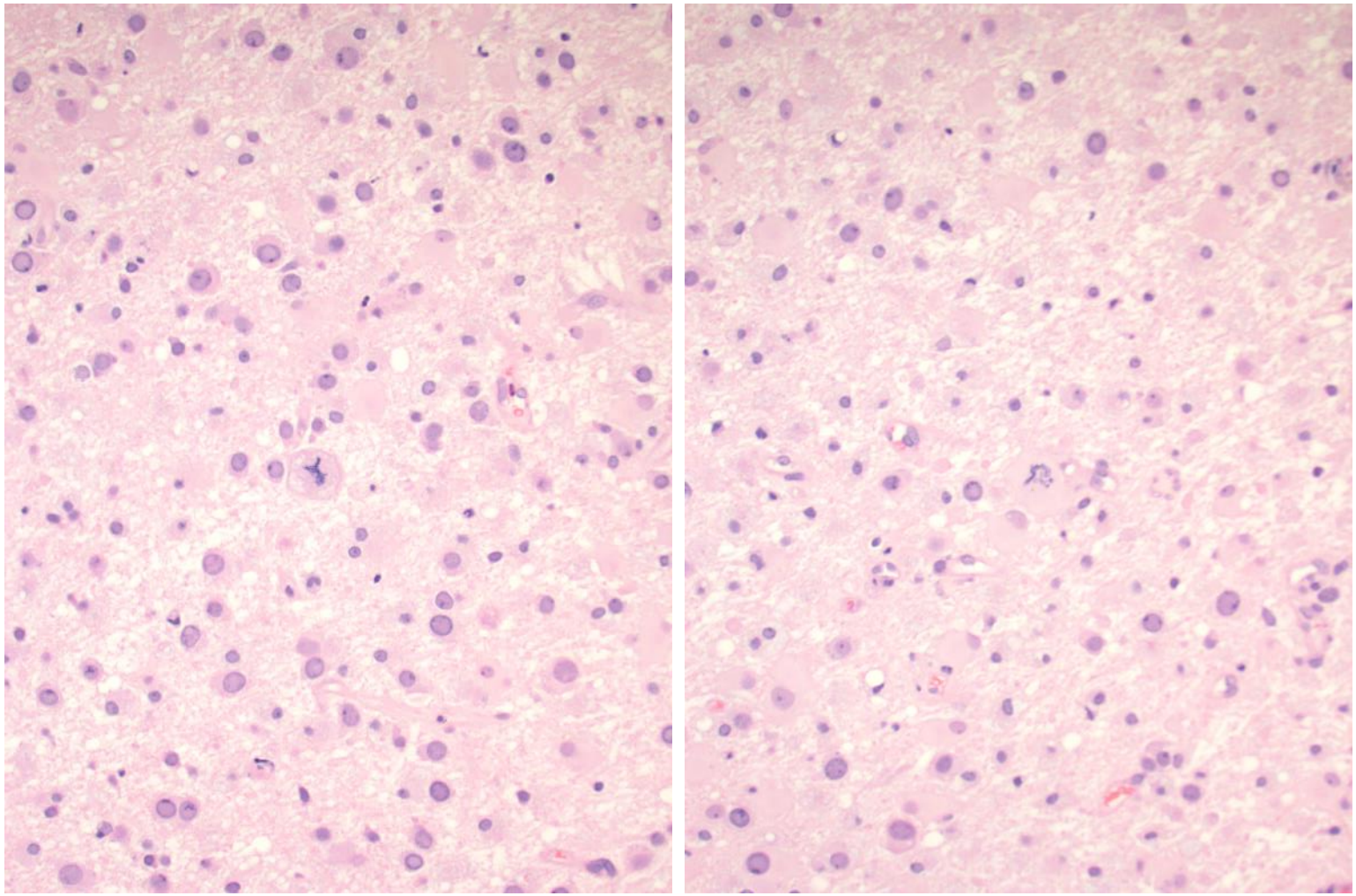


PML



PML

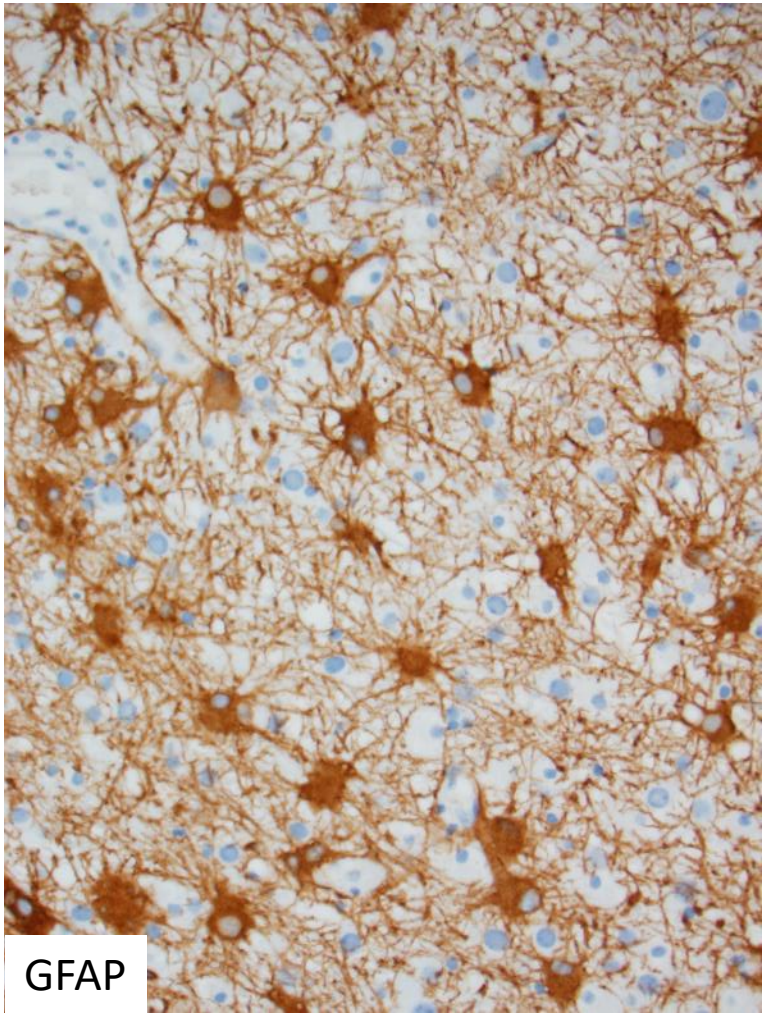
Histology- mitoses



PML

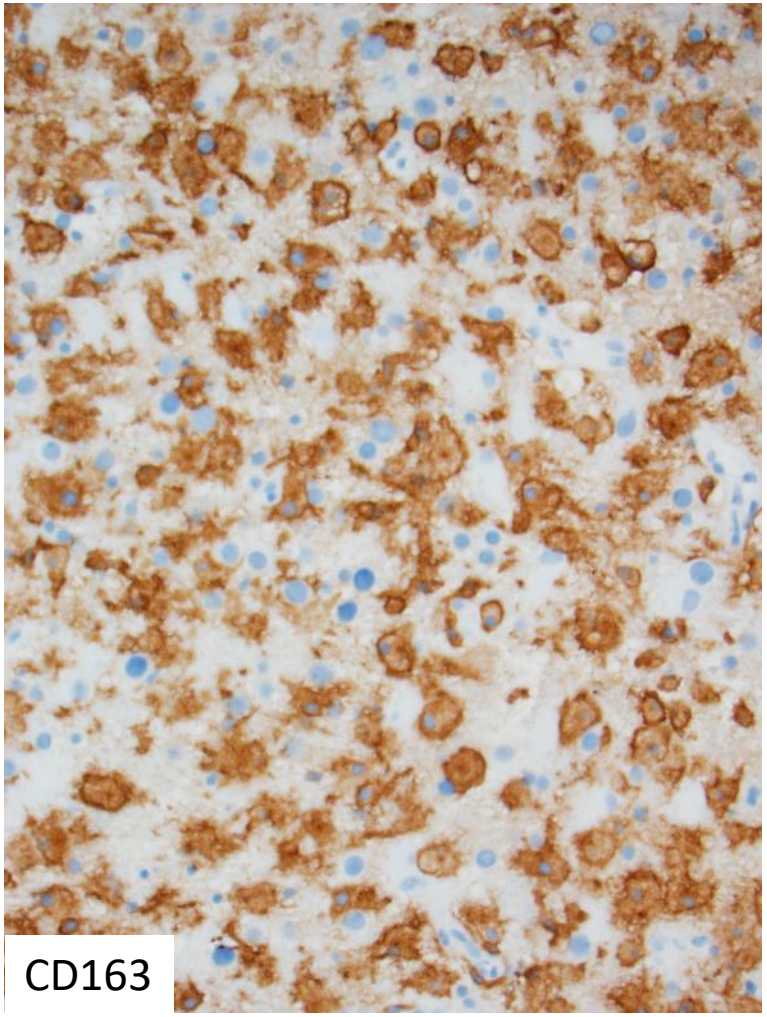
Histology

Reactive astrocytes



GFAP

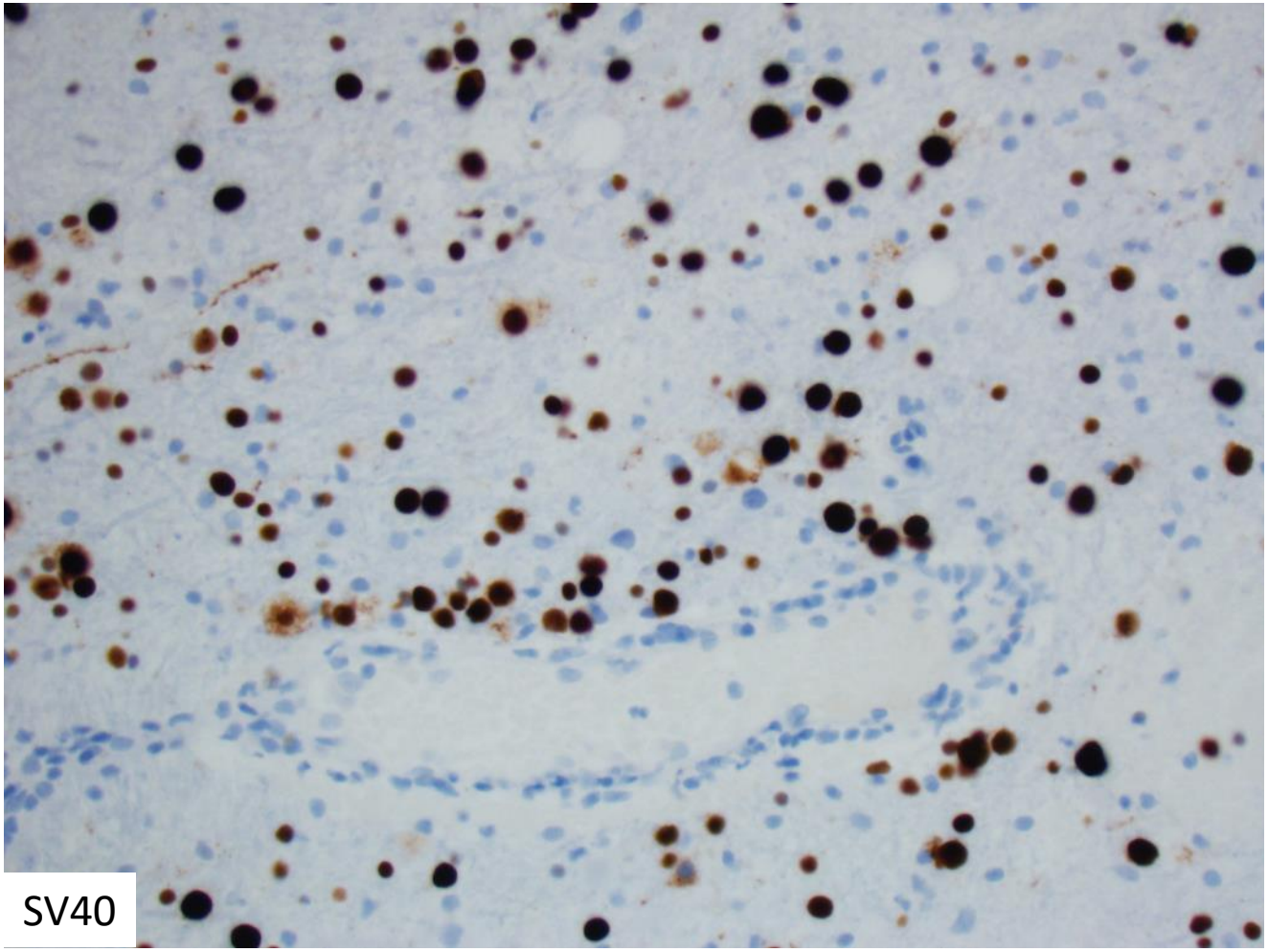
Macrophages



CD163

PML

Histology

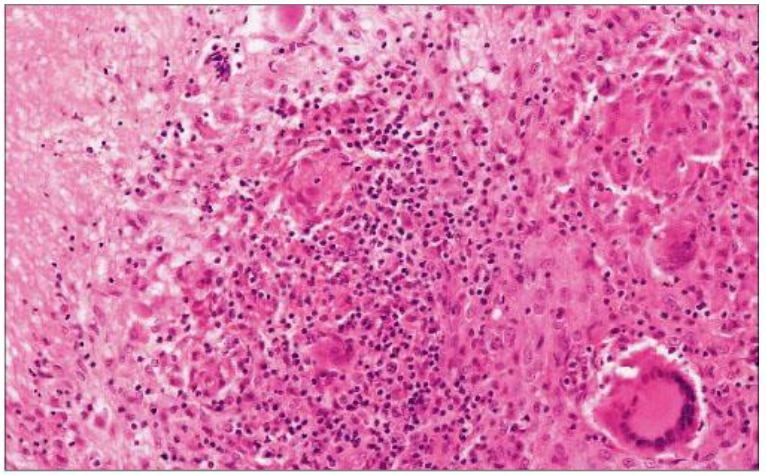


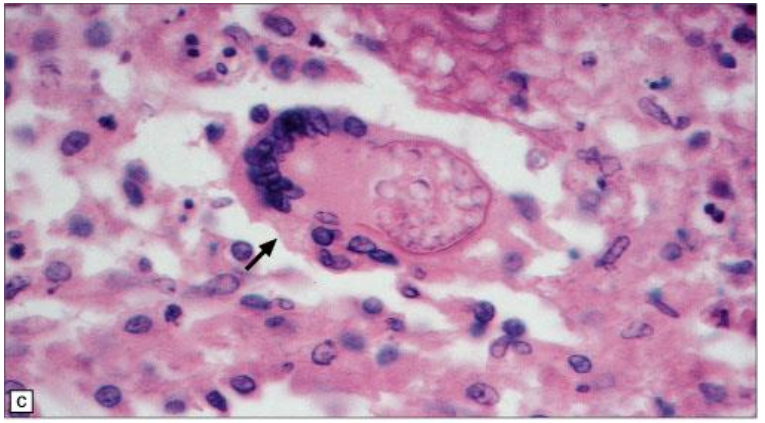
Bacterial/Fungal Infections

	Type of Infection	Organisms	Clinical History	Work-up
Bacteria	Meningitis	**Neonates**: Group B Strep, E. coli, Streptococcus pneumoniae **Pediatric**: *Strep. pneumo, N meningitides, H. influenza* **Adult**: all the above + *Listeria moncytogenes* and Gram-negative bacilli **Immunocompromised**: *Strep. pneumo, Mycobacteria*	Fever, photophobia, stiff/painful neck	Gram, GMS, PAS-Fungus, AFB
	Abscess	*Staphylococcus aureus* *Streptococcus viridans* *Bacterioides* sp.	Neurologic symptoms dependent on location	Gram, GMS, PAS-Fungus, AFB
Fungus	Meningitis	*Cryptococcus* (immunocompromised), *Coccidioides, Blastomyces*	Fever, photophobia, stiff/painful neck	Gram, GMS, PAS-Fungus, AFB
	Abscess	*Cryptococcus* (immunocompetent), *Aspergillus, Mucor*	Neurologic symptoms dependent on location	Gram, GMS, PAS-Fungus, AFB

Mycobacterium tuberculosis

- Microscopy shows **giant-cell granulomatous inflammation with caseating necrosis**
- Other findings:
  - Inflammation can lead to fibrinoid necrosis in veins and arteries
  - Endarteritis obliterans
- Fungi That Can Be Associated with Necrotizing Granulomas
  - Cryptococcus
  - Blastomyces
  - Coccidioides
  - Aspergillus





Parasites

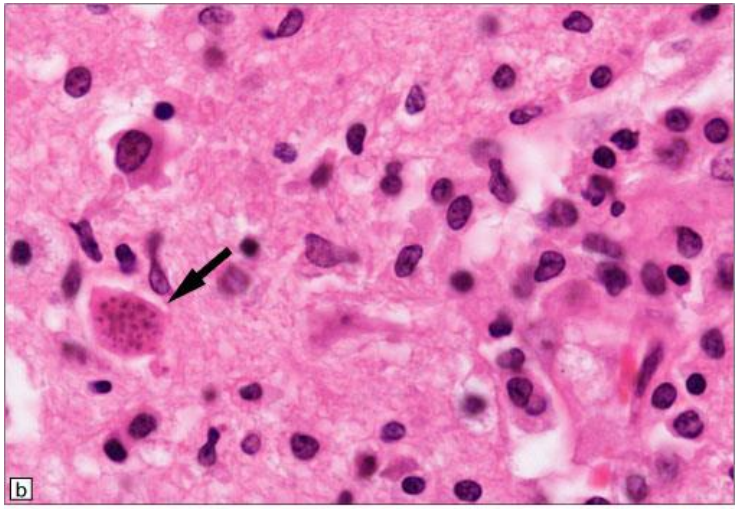
	Species	Environment/History	Work-up
Toxoplasmosis	*Toxoplasma gondii*	Cats are definitive hosts. Vulnerable: heme malignancies, BM/solid organ transplant, HIV/AIDS, immunocompromised	Identify bradyzoites Toxo IHC
Neurocysticercosis	*Taenia solium*	Eating pork infected by viable larvae or cysticerci. Industrialized nations: Typically immigrants from endemic areas (Cent. America in US)	H&E
Amoebiasis	Primary amoebic meningoencephalitis (PAM): *Naegleria fowleri* Granulomatous amoebic encephalitis (GAE): *Acanthamoeba* sp., *Balamuthia mandrillaris*	PAM: Playing in warm, fresh water. Rapid progression from seizures to coma, death within a week GAE: Targets malnourished, debilitated, chronically ill, immunocompromised; similar to any space-occupying lesion; location dictates symptoms	H&E Send to CDC for definitive species identification

Toxoplasmosis

Abundant necrosis

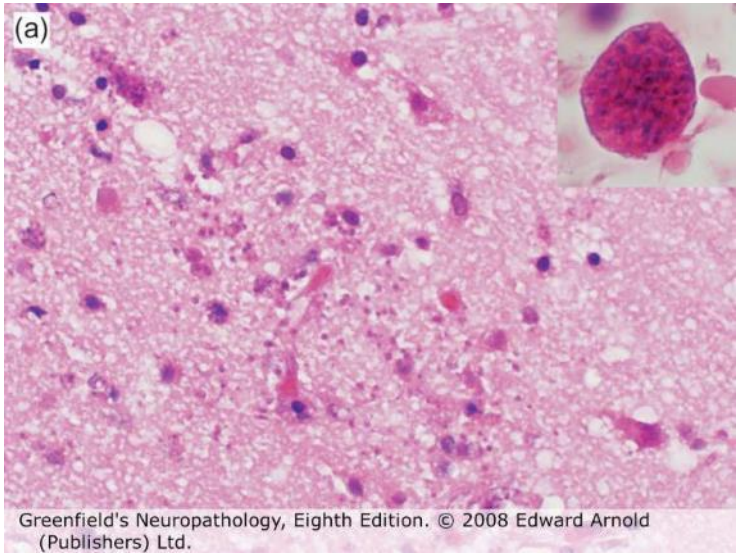
Greenfield's Neuropathology, Eighth Edition. © 2008 Edward Arnold (Publishers) Ltd.

Bradyzoite



Ellison & Love: Neuropathology 2e © 2004 Elsevier Ltd.

Tachyzoites



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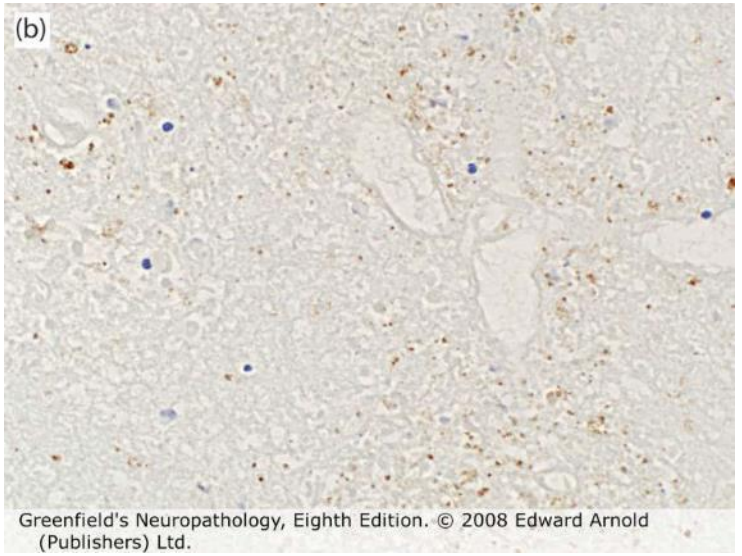
Toxo IHC



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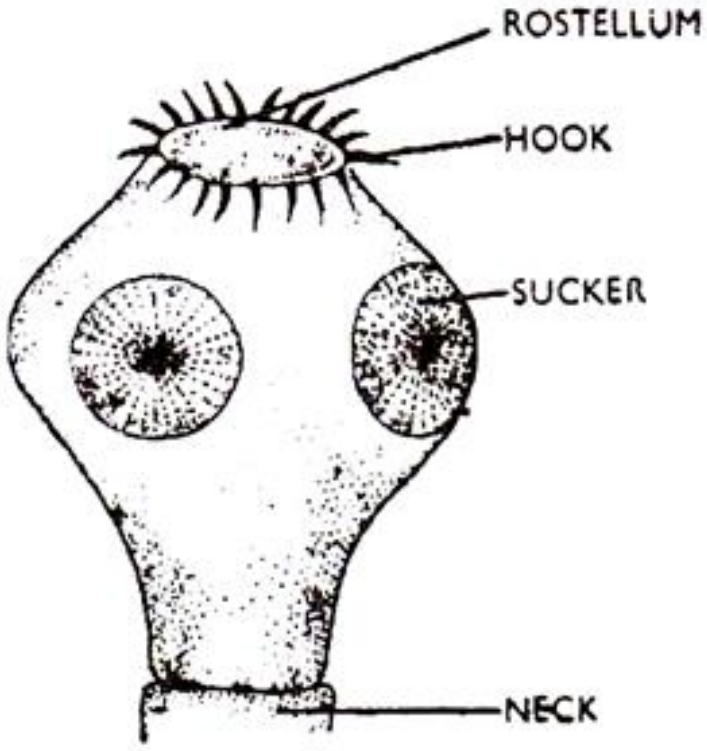
Cysticercosis

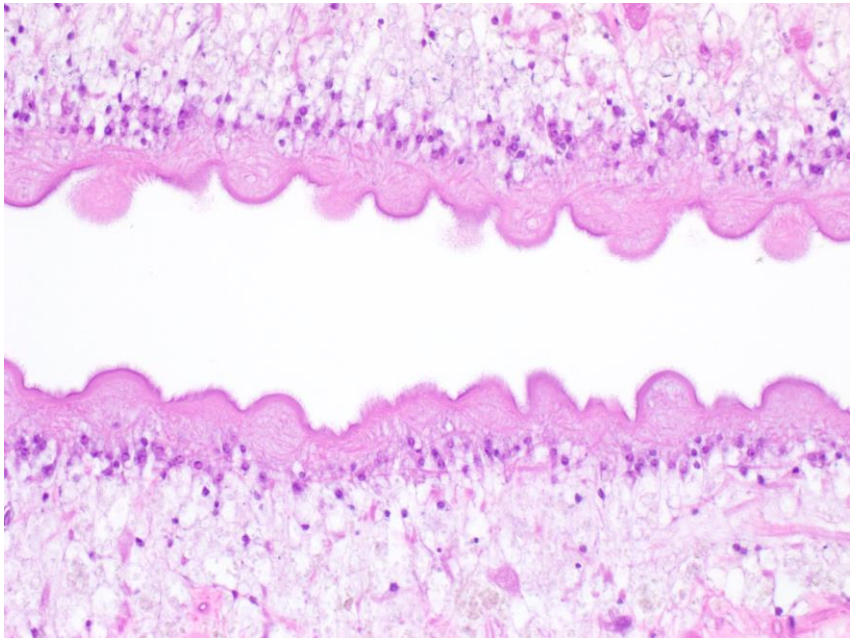


From biologydiscussion.com

Scolex with hooks and suckers (arrow)

From CDC.gov

Outer surface= wavy eosinophilic lamina



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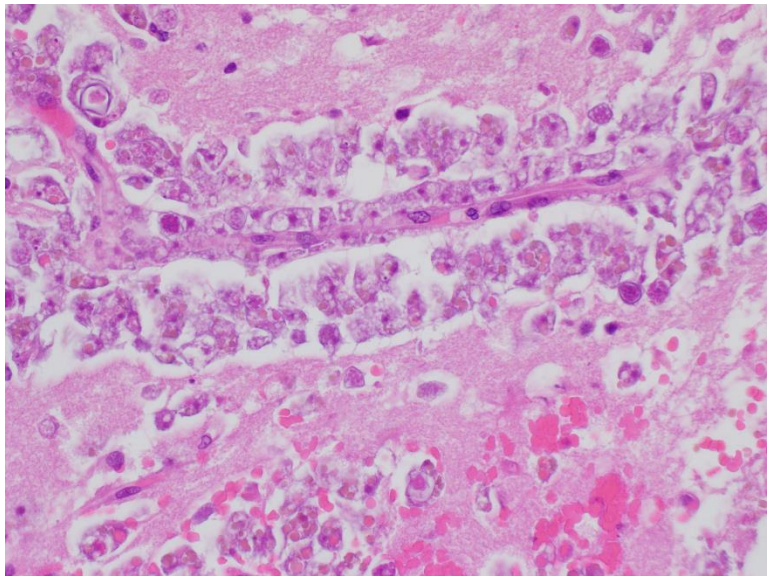
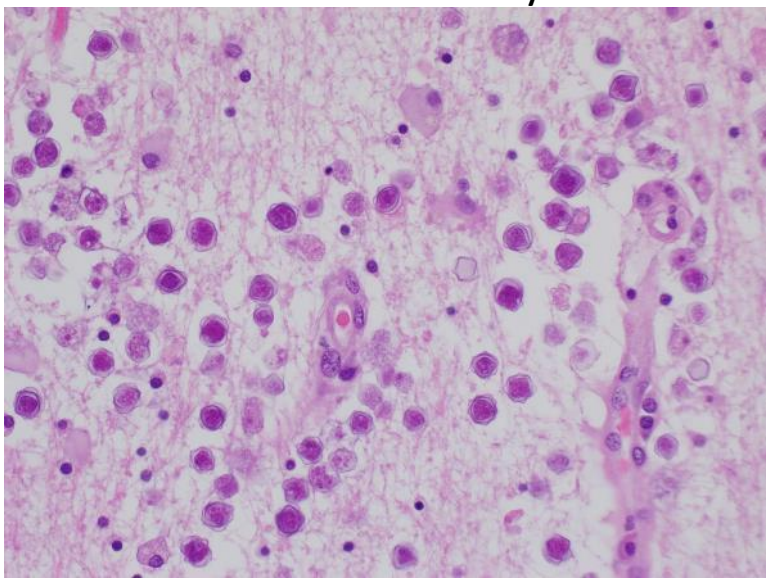
Amoebiasis

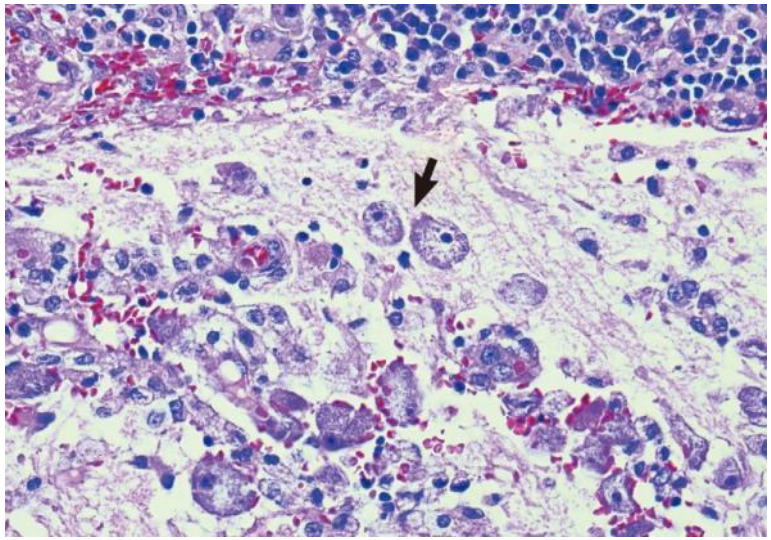
Perivascular *Acanthamoeba*



Acanthamoeba cysts

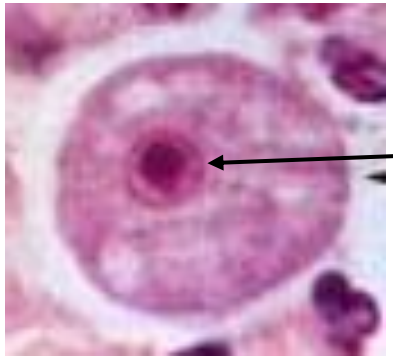


Balamuthia mandrillaris



From ResearchGate

Naegleria fowleri



From med-chem.com

- Amoeba can mimic macrophages.
- Note the small nucleus with large **karyosome**.
- *Balamuthia* karyosomes are less prominent.

Leukocyte-rich lesions

'Day-of-frozen-section' special requests

- Lymphocytic Infiltrate?
  - Flow cytometry
- All inflammatory lesions
  - Broad microbial cultures (aerobe, anaerobe, fungal, AFB)

Thank you!

Please contact me at christian.davidson@path.utah.edu with any questions.