AANP 67th Annual Diagnostic Slide Session: Case #2

Presenter: Dr. Katie DiScipio MD, PhD

AP/CP Resident, PGY3

Mentor: Dr. Suzanne Powell MD

Neuropathology Attending

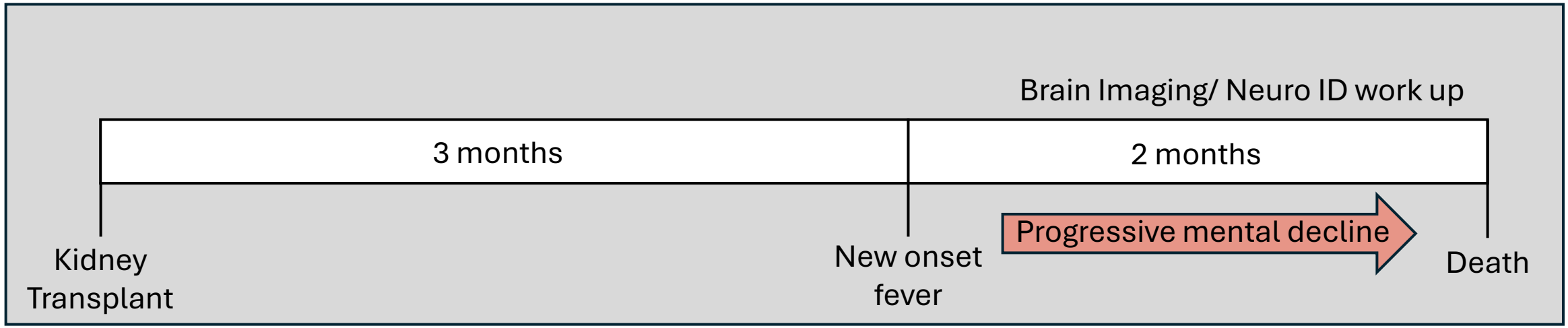
Professor of Pathology and Genomic Medicine

HOUSTON Methodist LEADING MEDICINE

Department of Pathology and Genomic Medicine

Clinical History

- 62-year-old female status post kidney transplant for end stage renal disease secondary to type 2 diabetes who presented with **new onset fever** (3 months post-transplant).
- She exhibited vague neuropsychiatric symptoms including: **intermittent headache, withdrawn/flat affect, decreased verbal fluency, irritability, poor eye contact, proximal weakness, and decreased mobility.** This ultimately progressed to **encephalopathy**.
- After 2 months of hospitalization, she died with severe sepsis, coagulopathy, multiorgan dysfunction, and clinical concern for hemophagocytic lymphohistiocytosis (HLH).



CSF studies

- Mild pleocytosis (WBC: 6/CMM, 83% lymphocytes)
- Hypoglycorrhachia (39 mg/dL)
- Elevated protein (100 mg/dL)

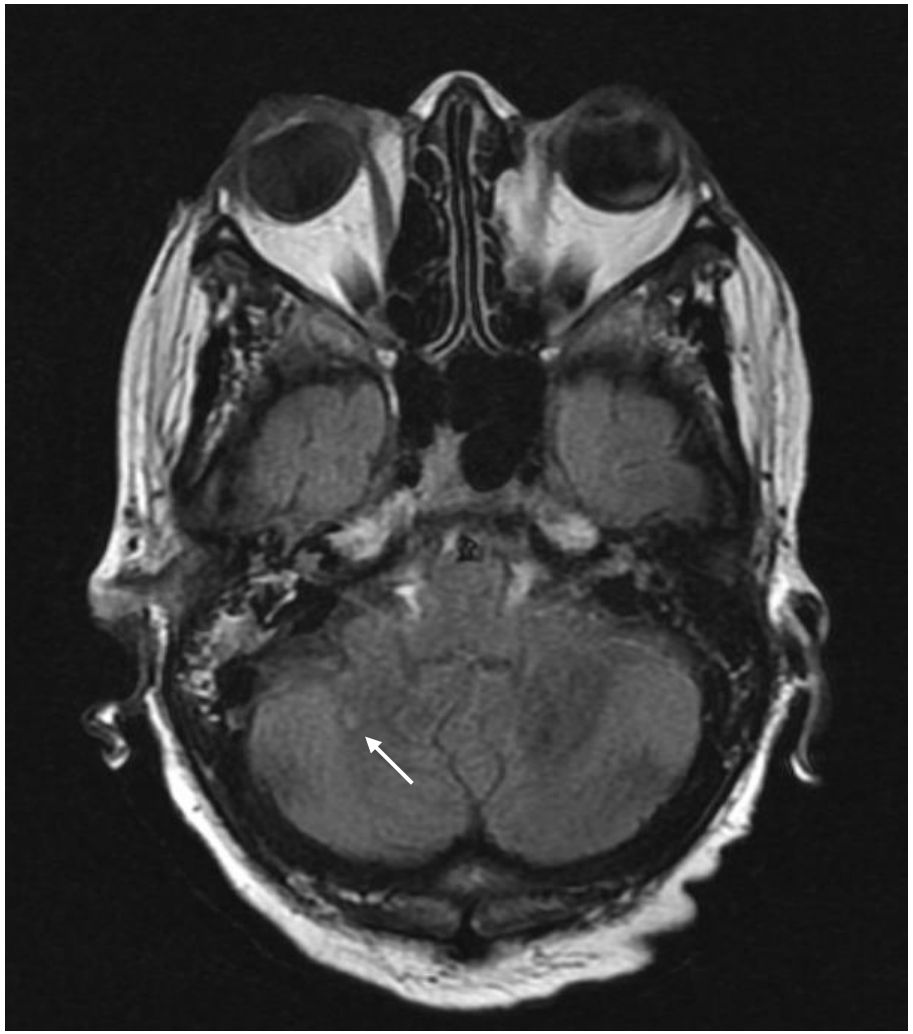
An extensive infectious work up was non-revealing

MRI Imaging (5 weeks post admission)

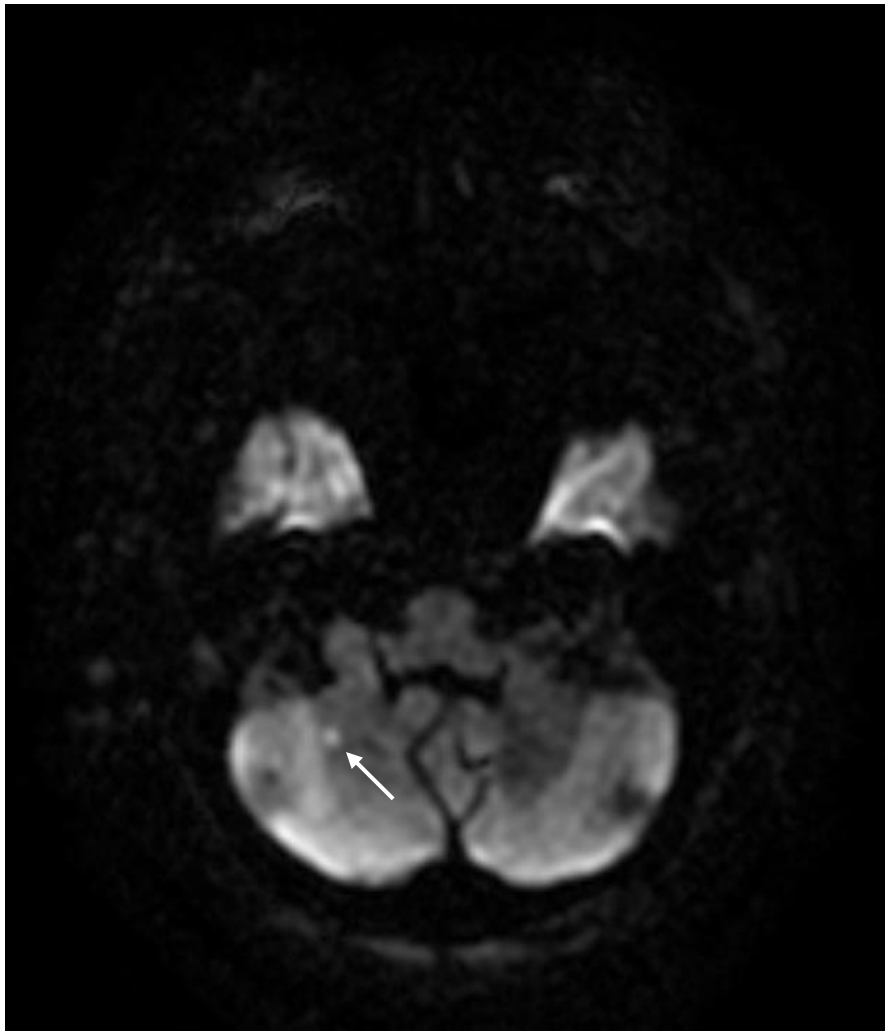
- A sub-centimeter focus of mild restricted diffusion was identified in the **right cerebellar hemisphere**, compatible with **acute/subacute infarct.**

- No other acute findings were seen on MRI or CT imaging of the brain

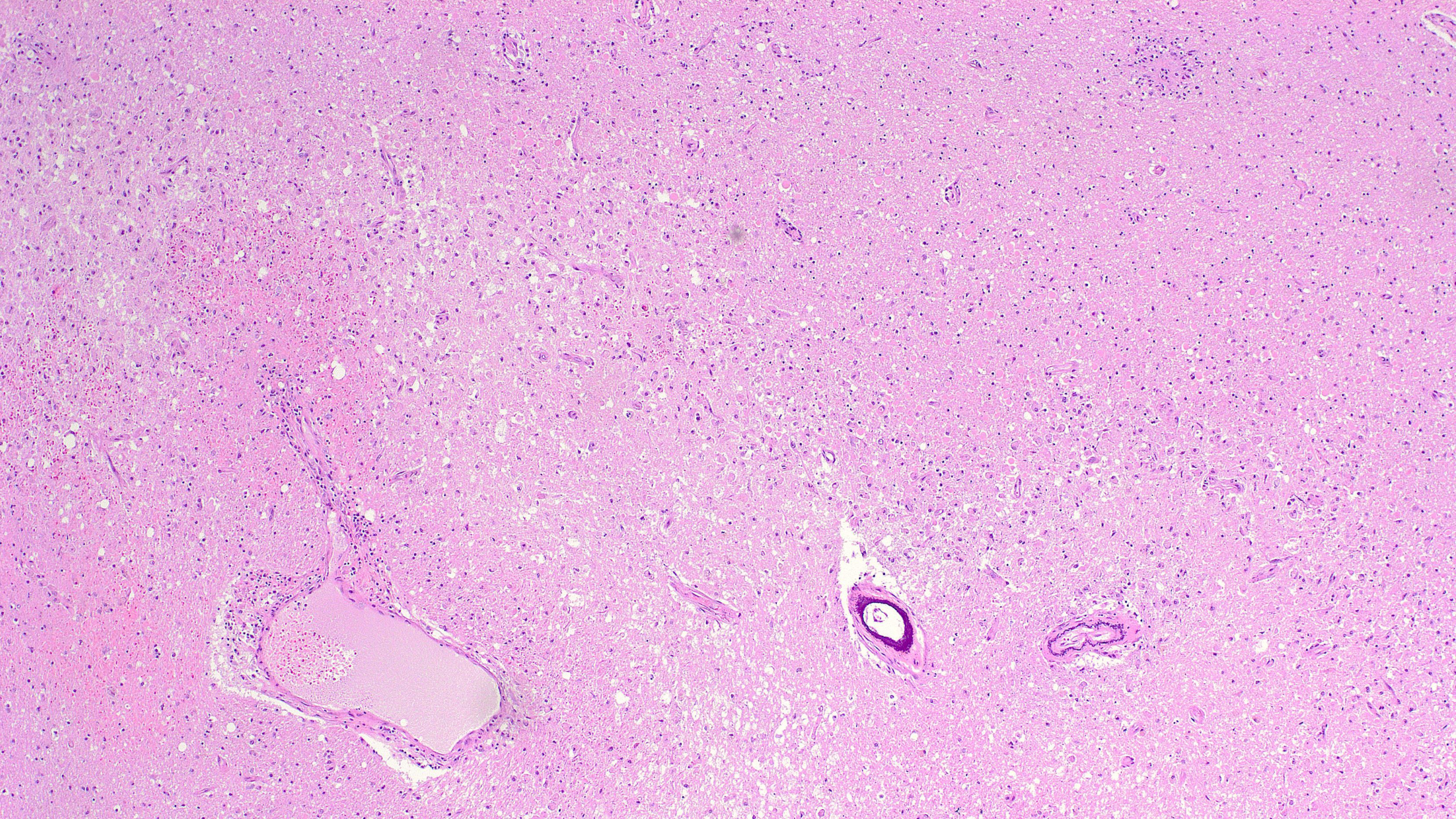
T2 FLAIR

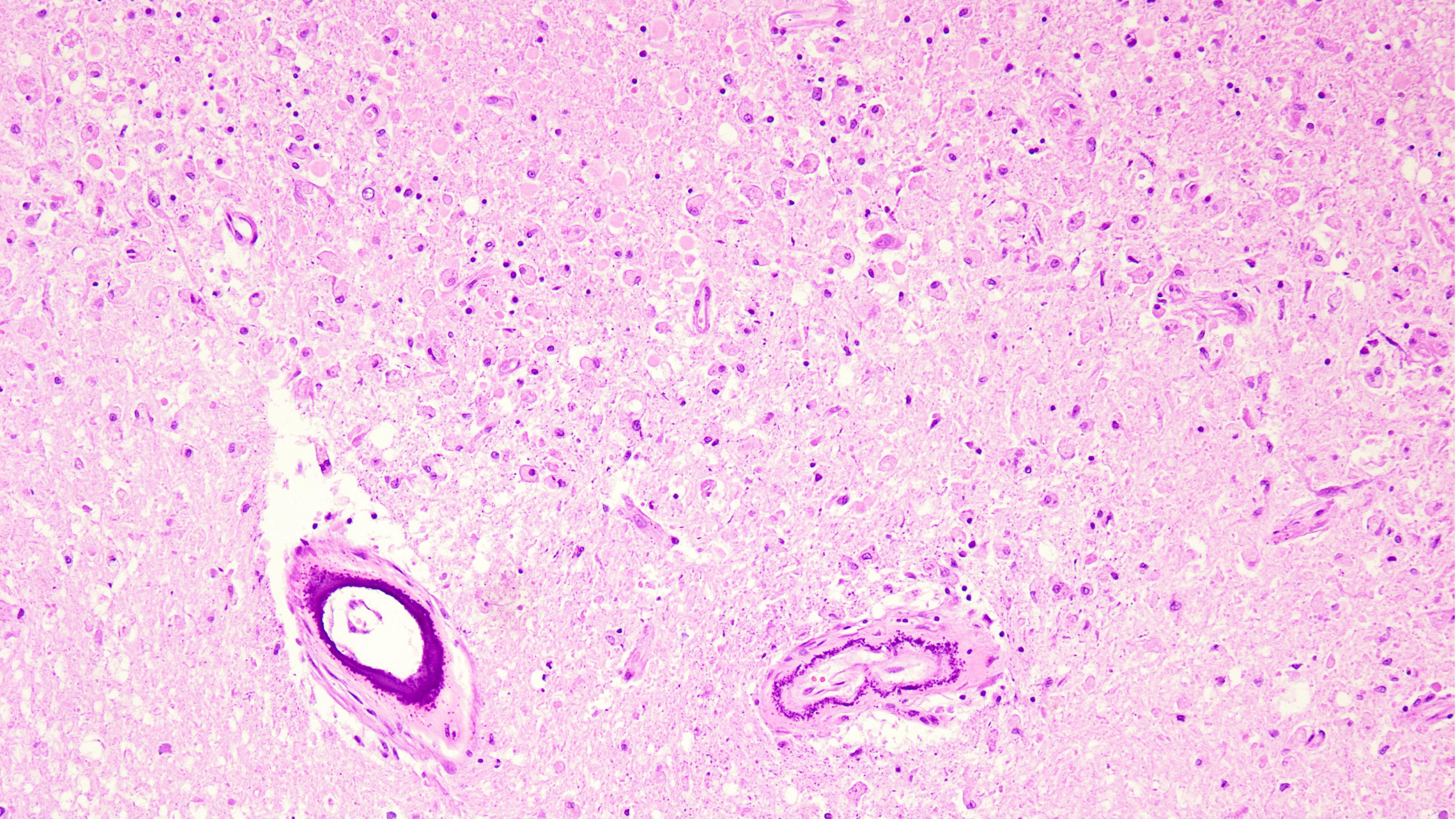


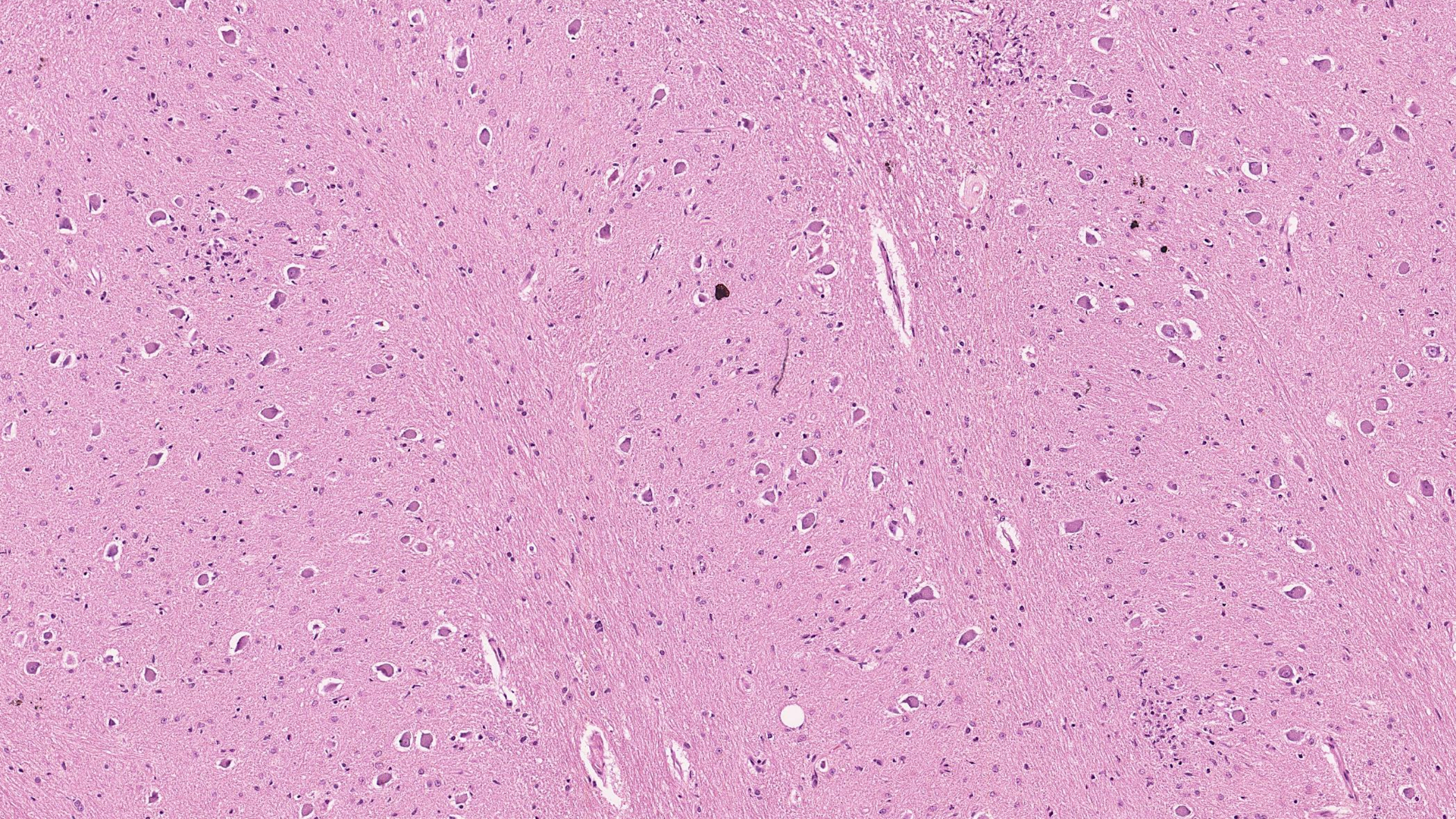
EPI DWI



Slides for Review





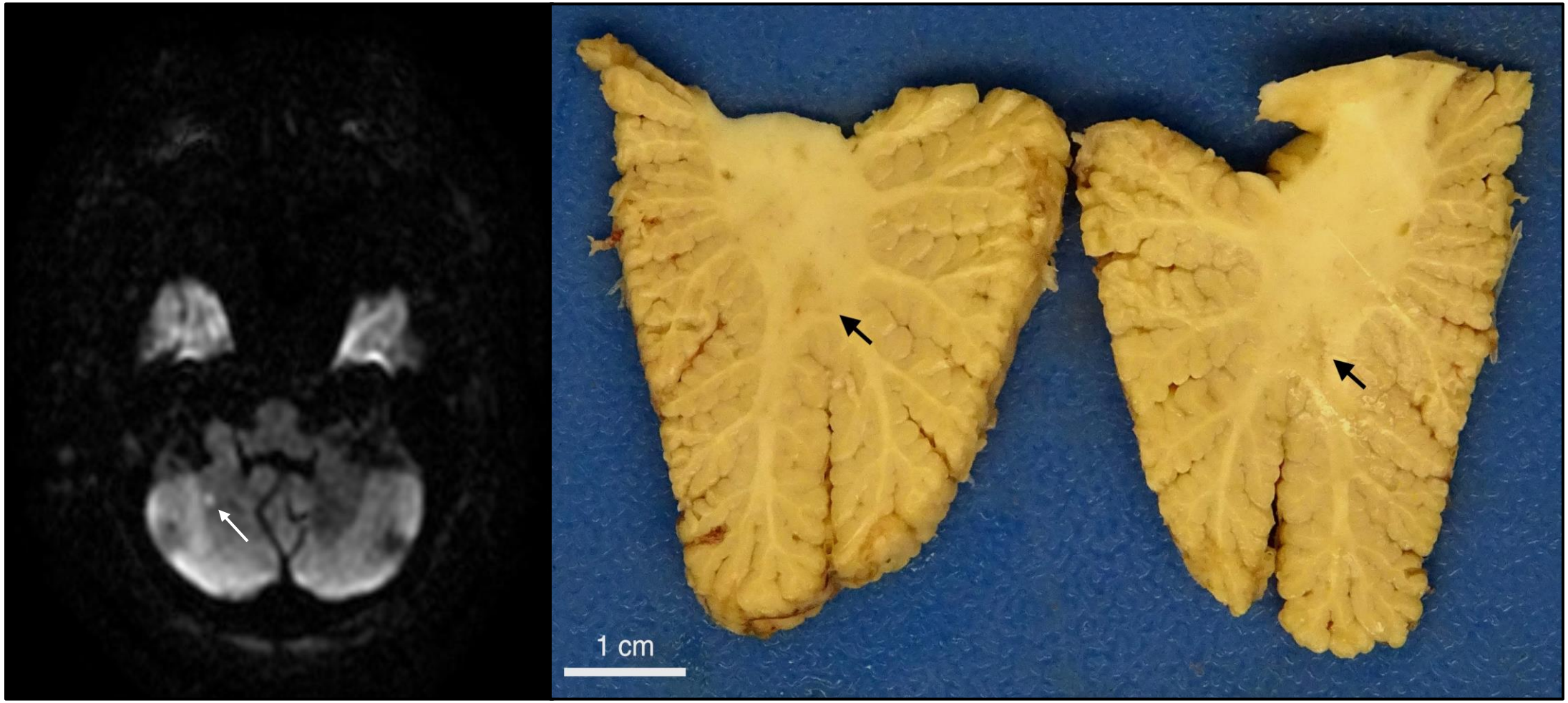


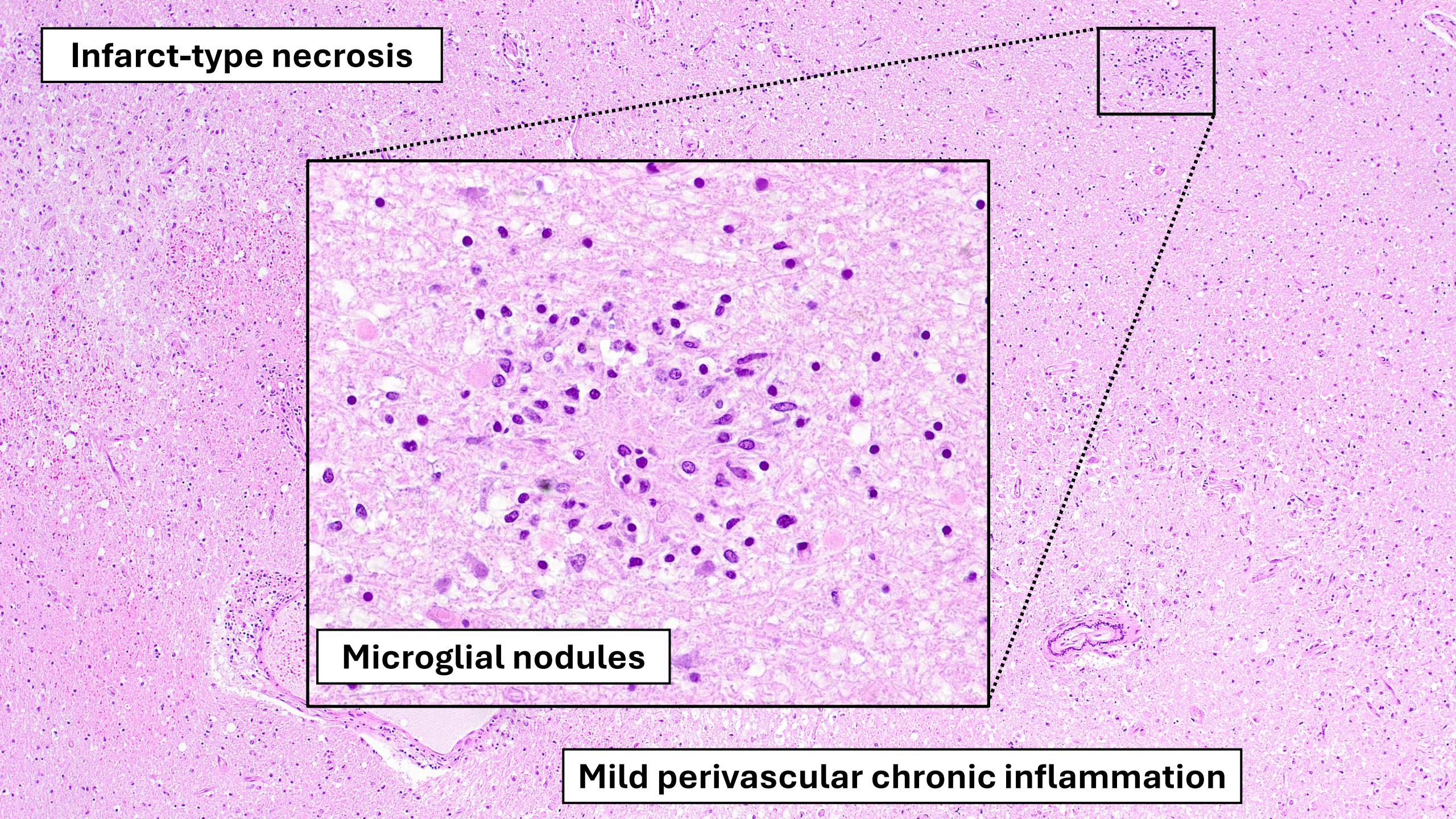
The case is now open for discussion:

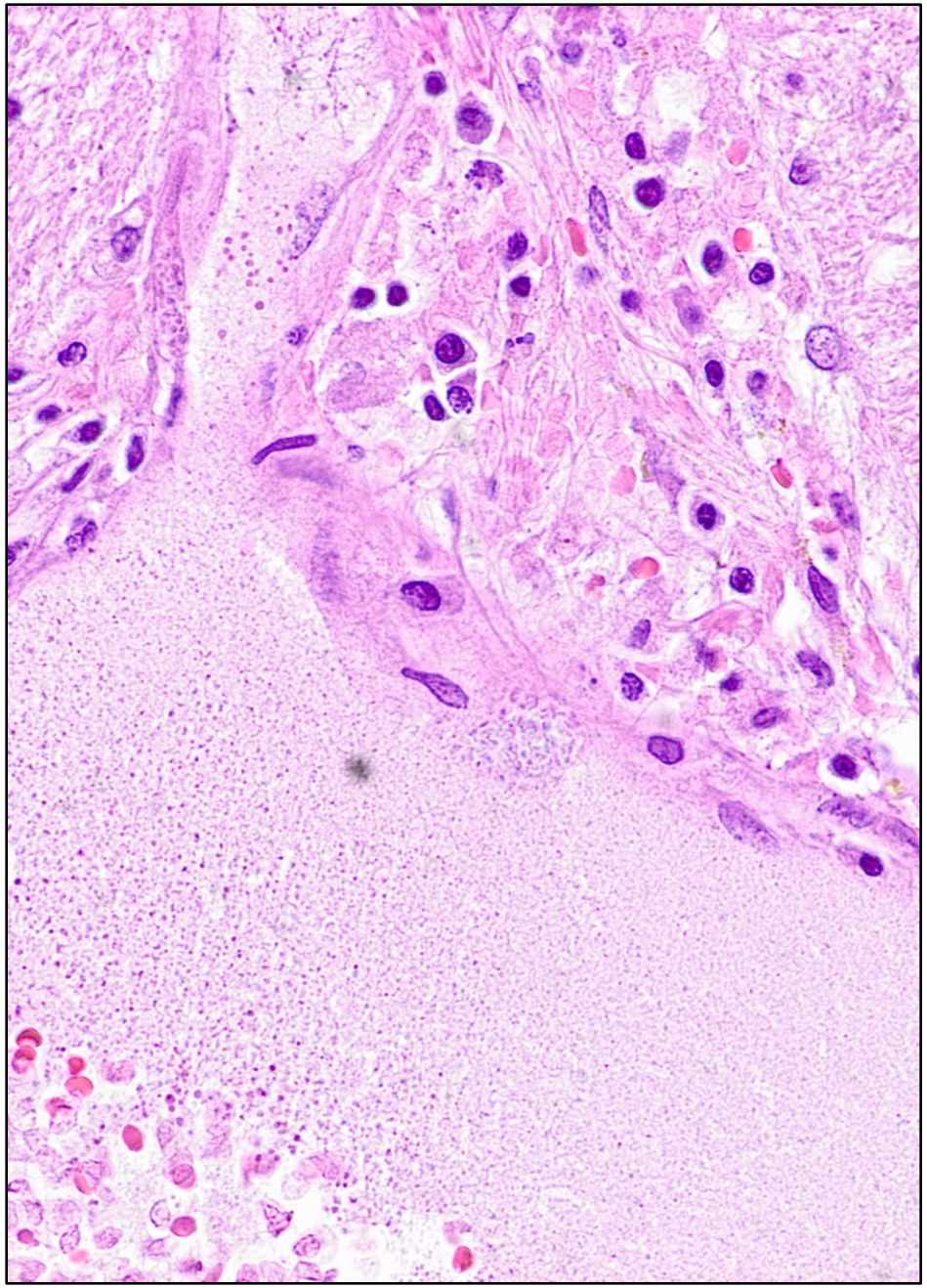
1.) Differential diagnosis?
2.) Additional ancillary testing?

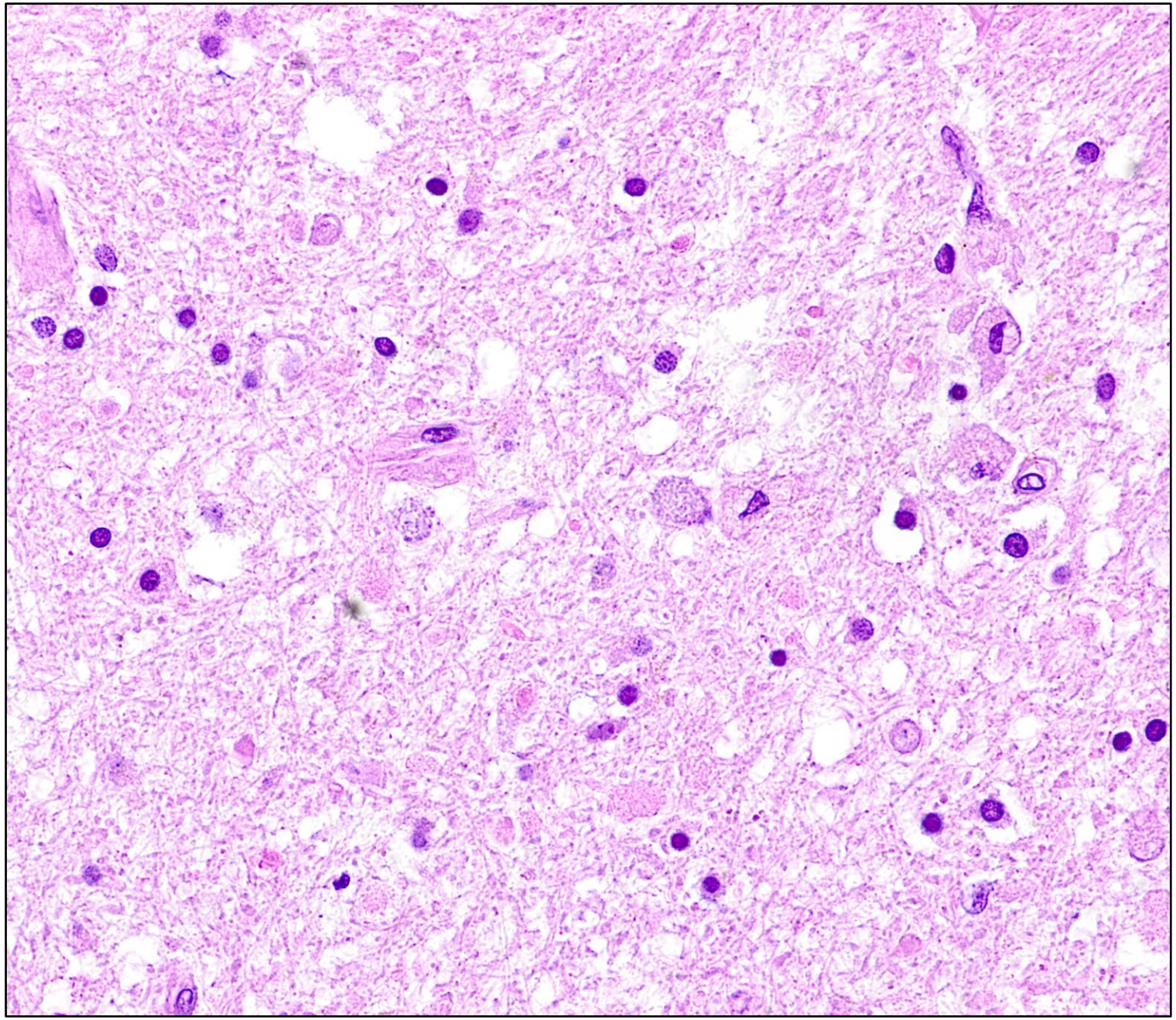
Gross examination of the brain at autopsy

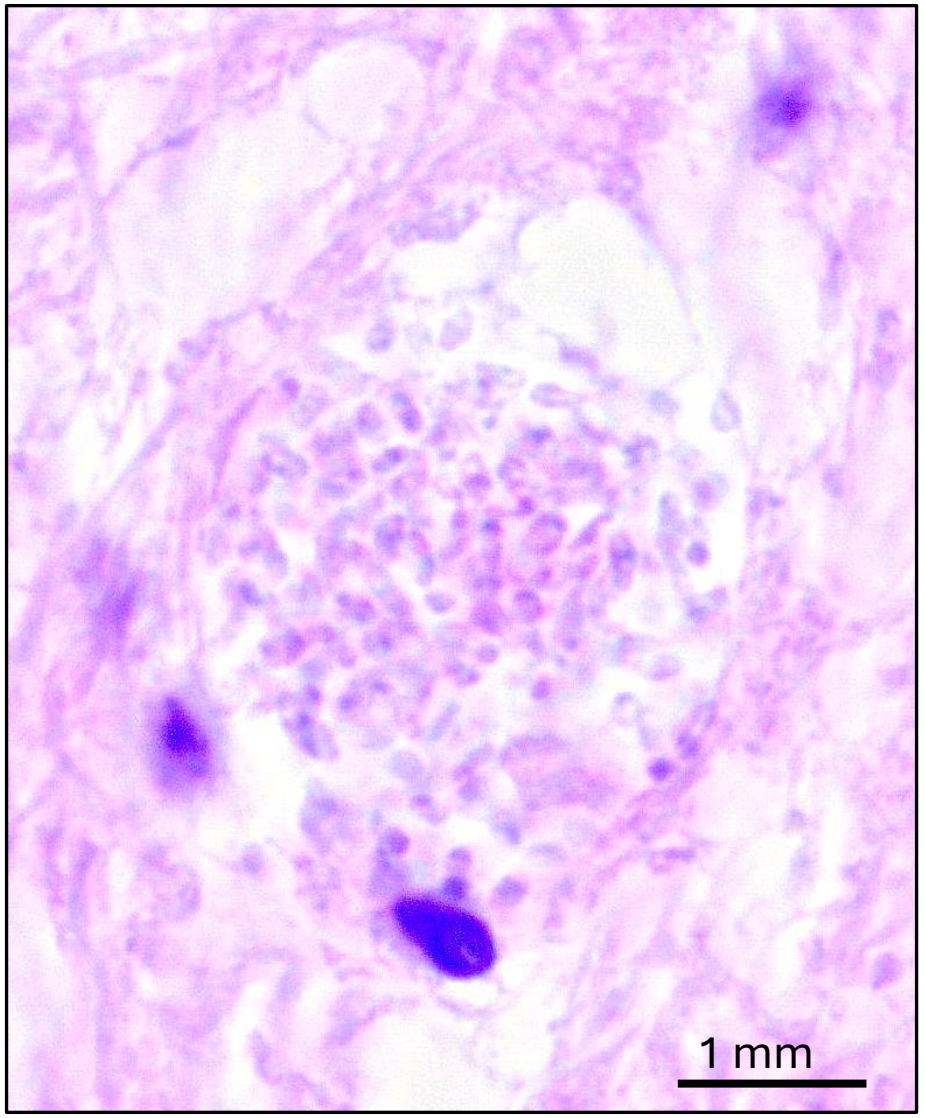
Area of softening was found in the white matter of the cerebellum corresponding to lesion seen on MRI




Infarct-type necrosis
Microglial nodules
Mild perivascular chronic inflammation







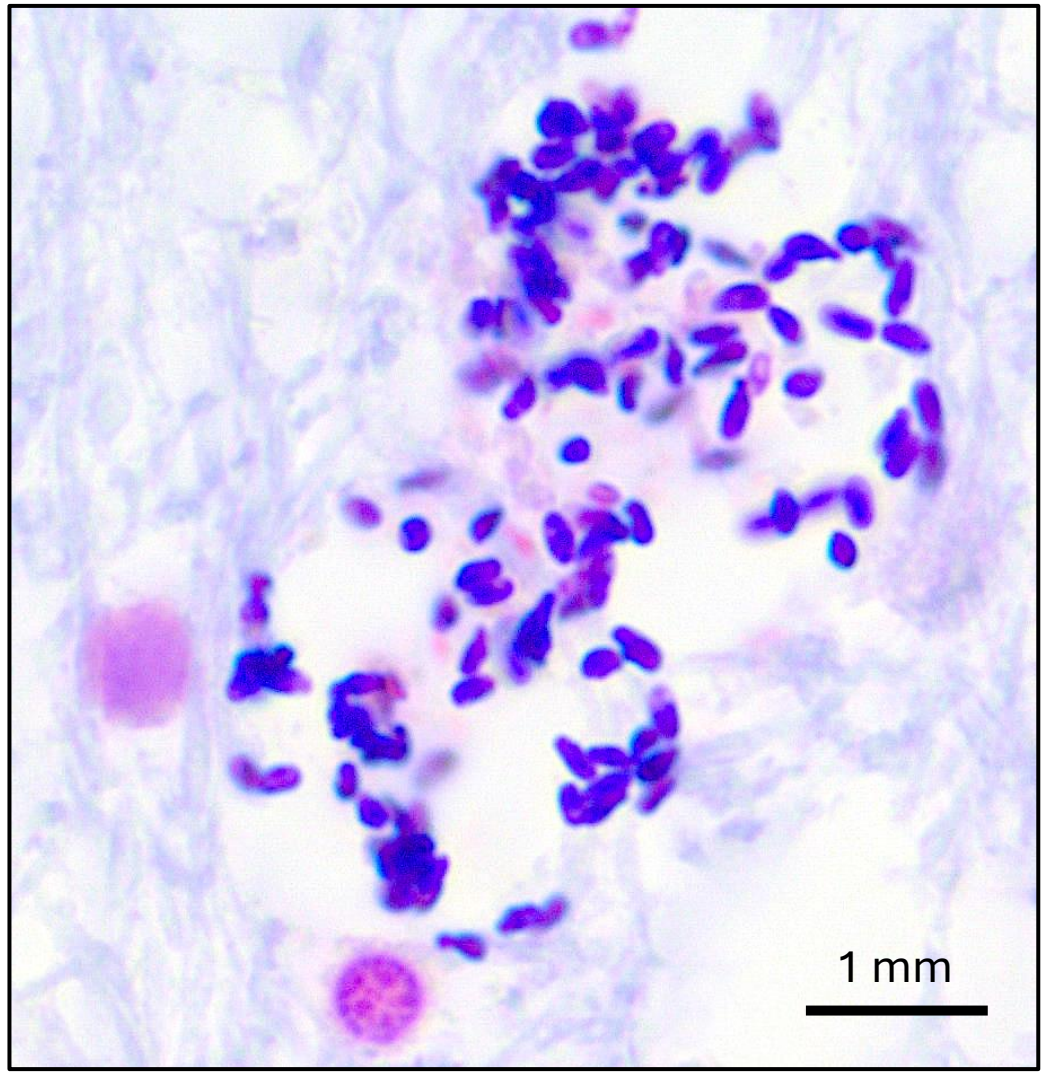
Macrophages

Glial cells

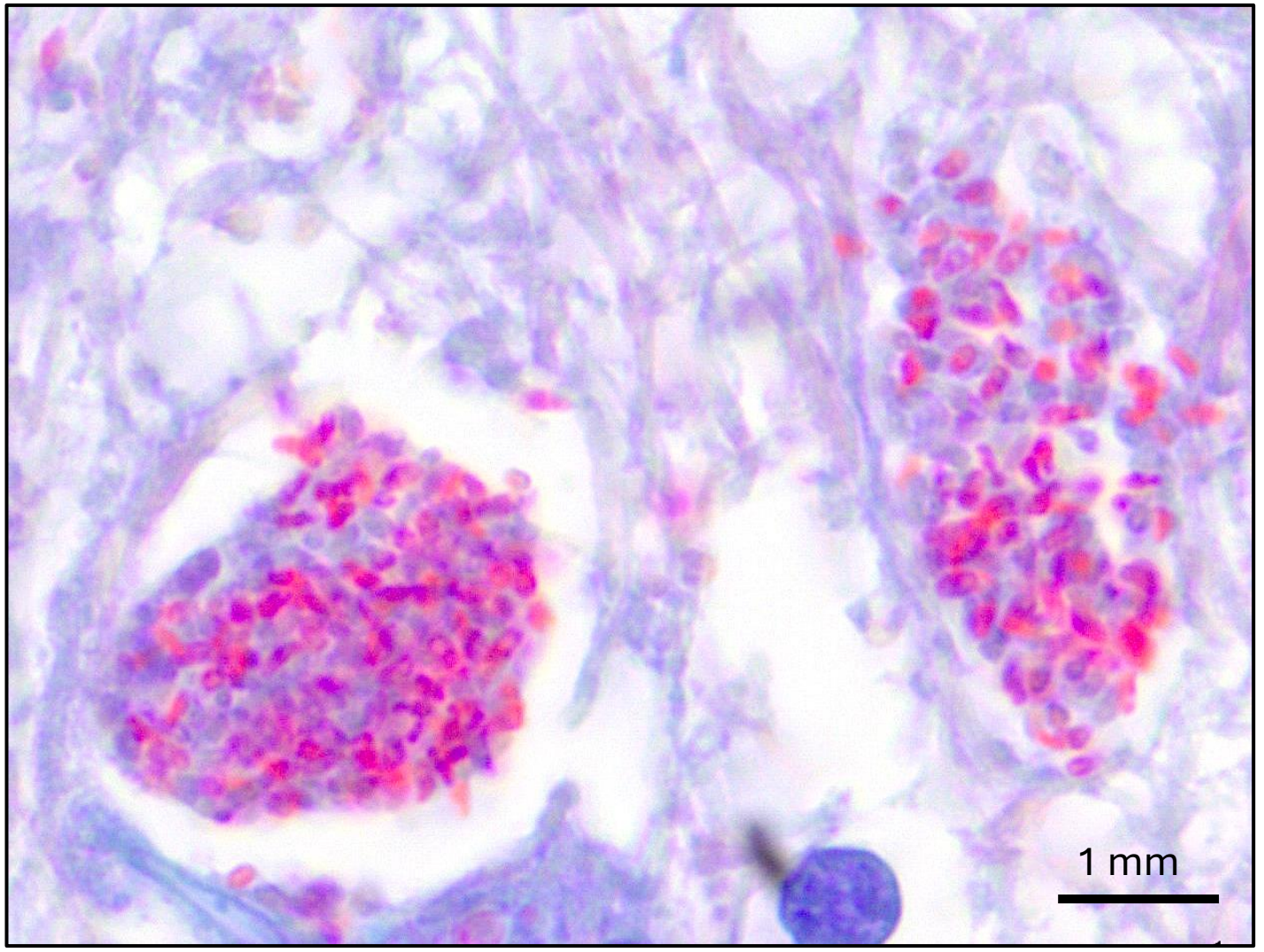
Vascular endothelial cells

Intravascular

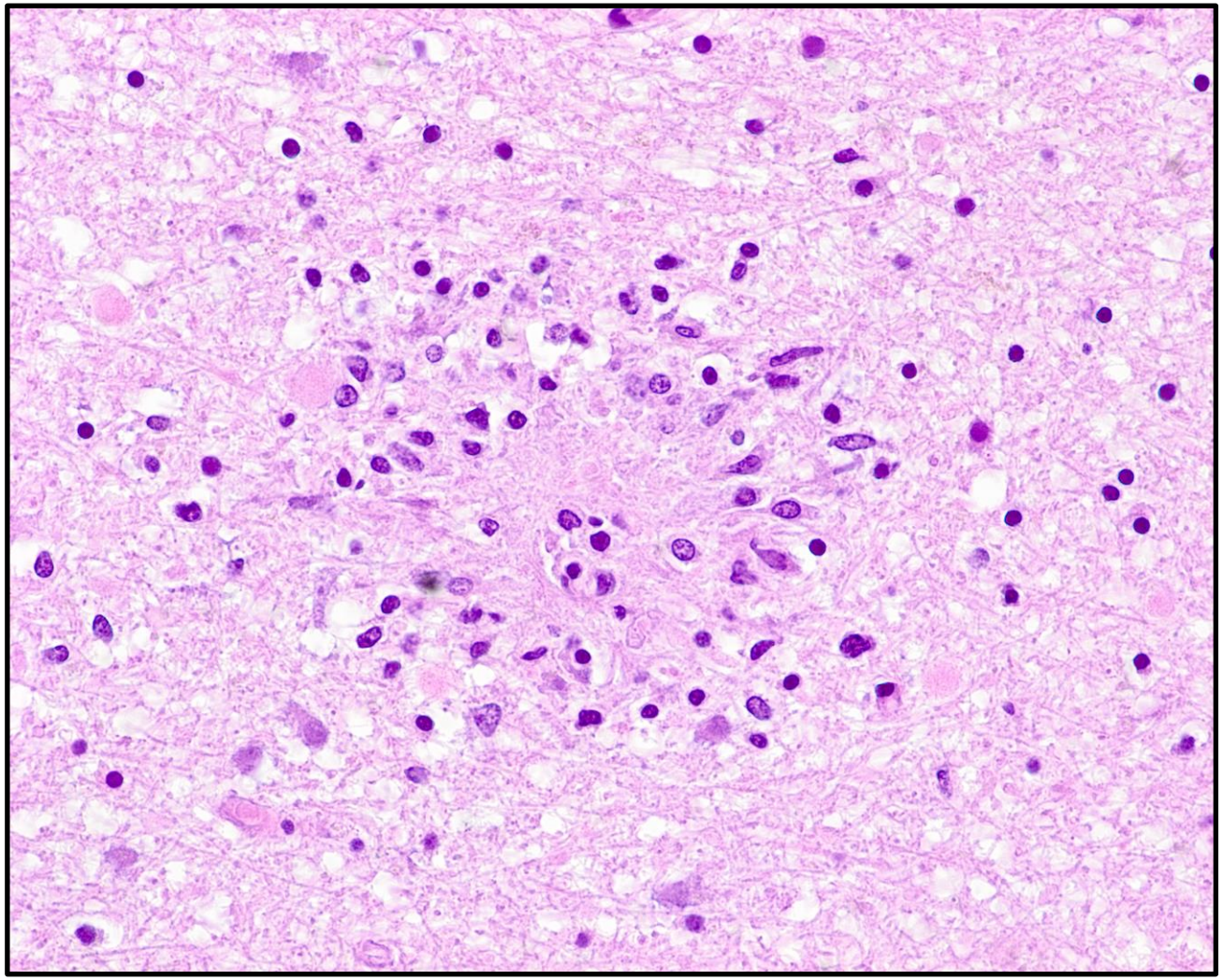
Tissue Gram Stain

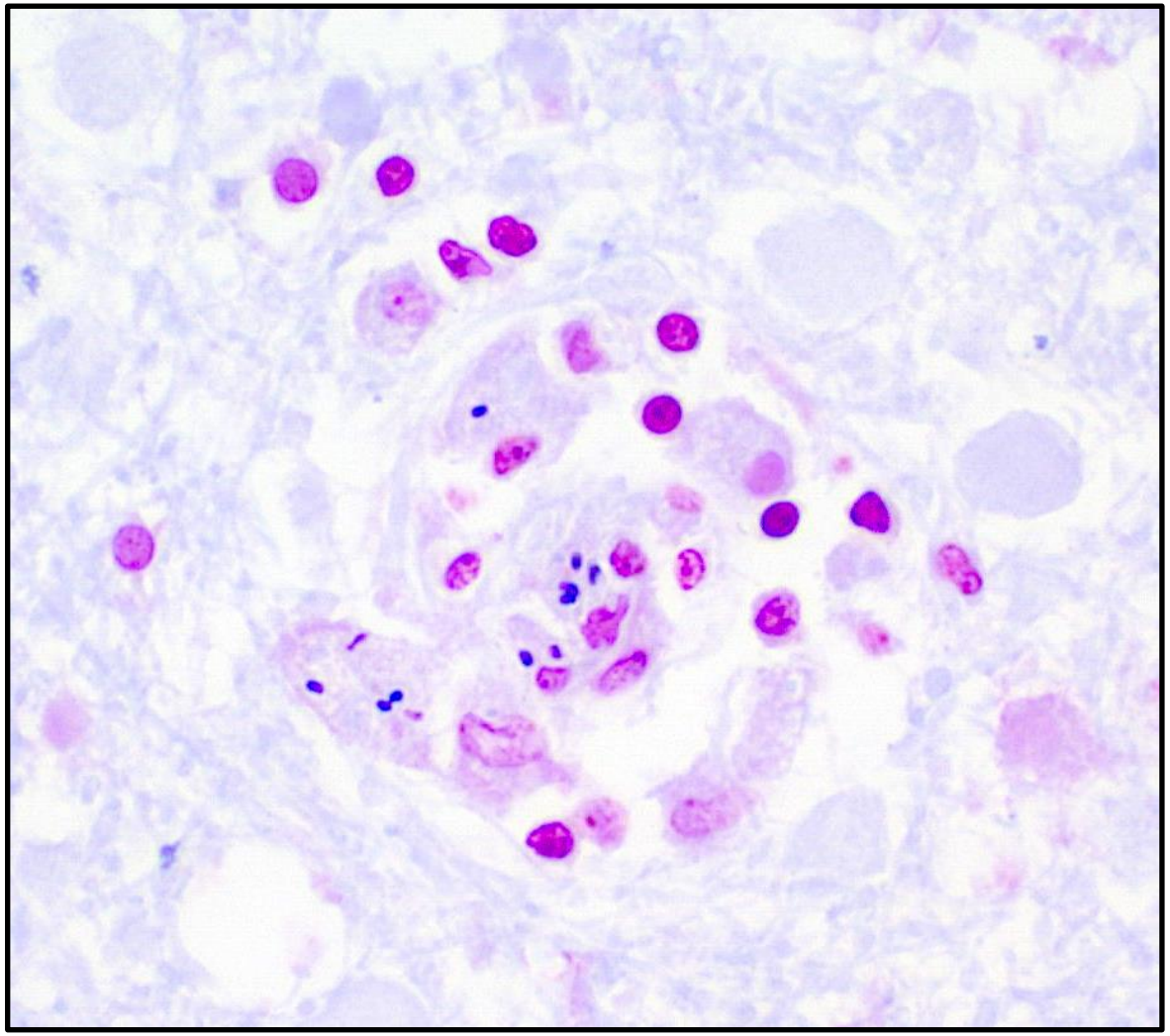


Modified Trichrome (Ryan-Blue)

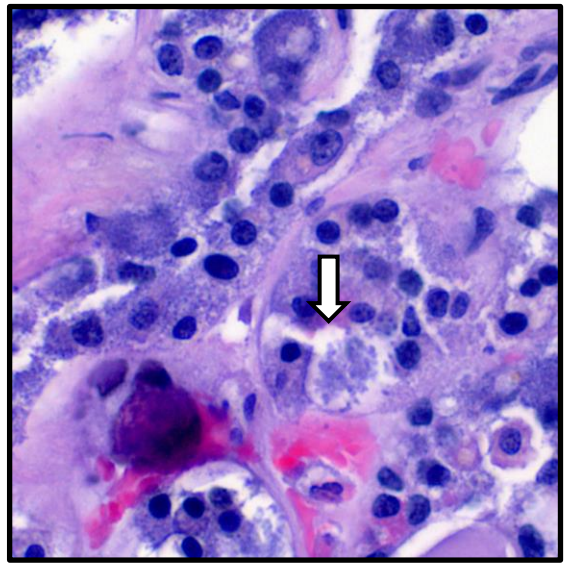


Rare organisms can be seen inside microglial nodules

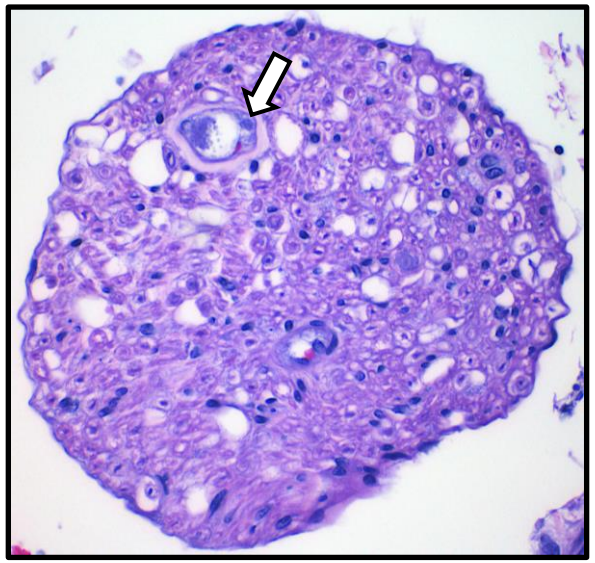




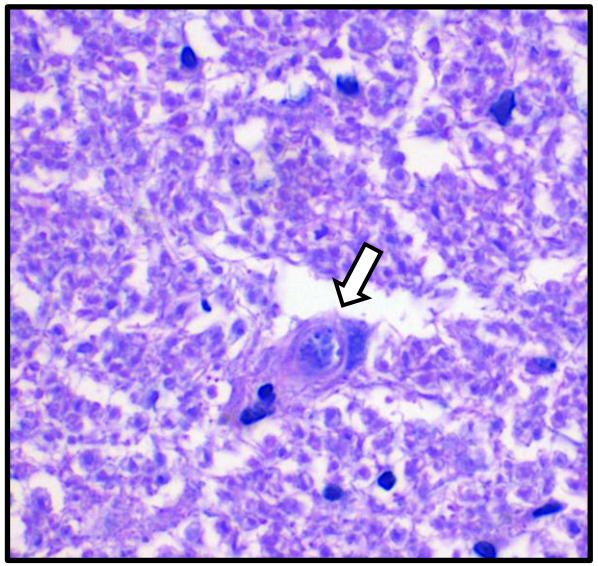
Pituitary
(Adenohypophesis)



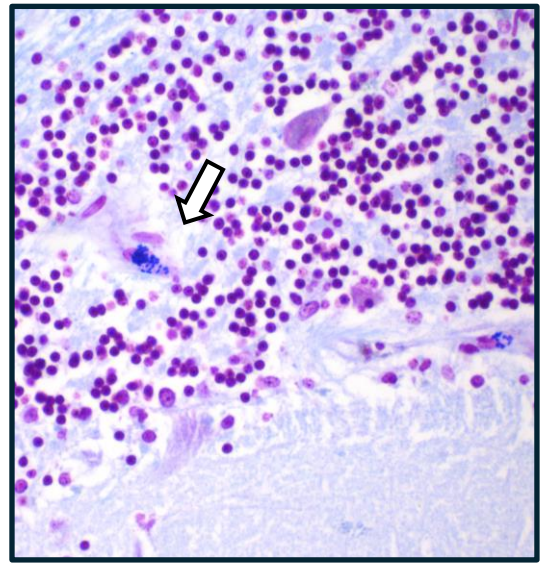
Nerve Root



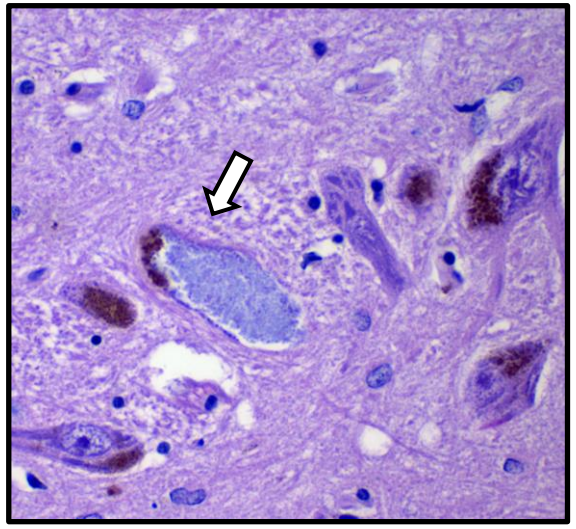
Spinal cord



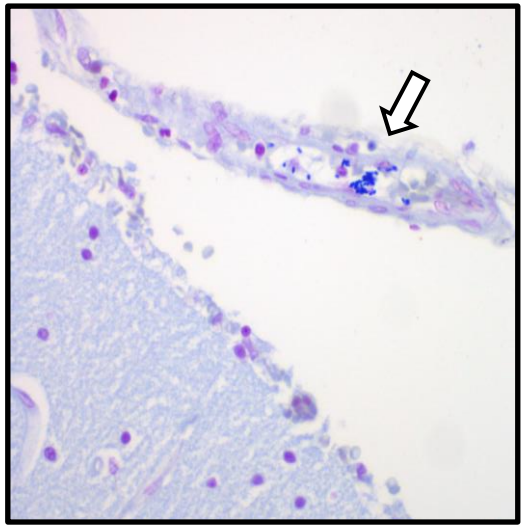
Cerebellum



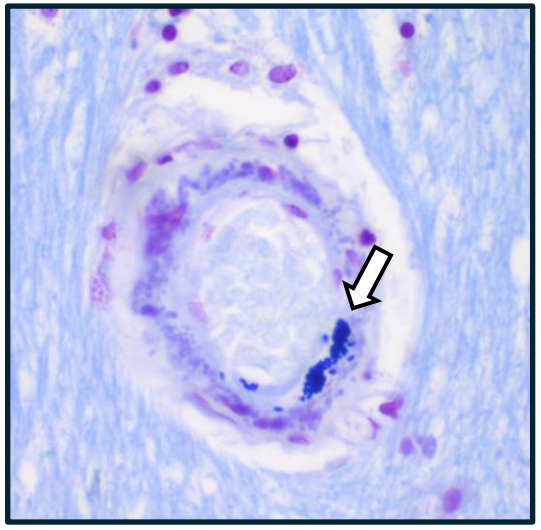
Midbrain
(Substantia Nigra)



Leptomeninges



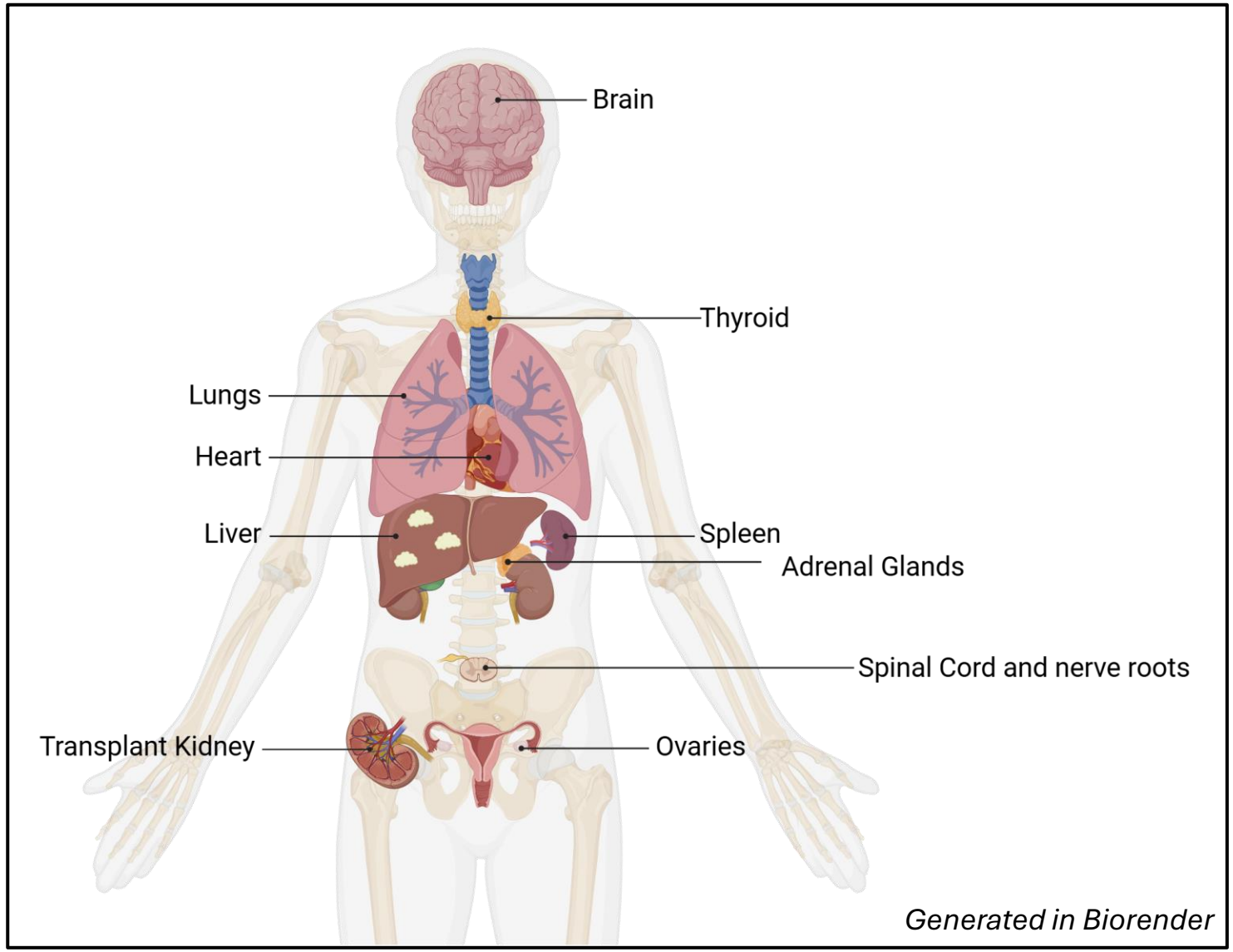
Parenchymal Vessels



Final Diagnosis

Disseminated microsporidosis with involvement of the CNS

Summary of affected sites seen at autopsy



Additional confirmatory studies

Molecular testing on pre-mortem specimens had been performed including:

- Universal PCR/NGS on FFPE tissue from a liver lesion biopsy (University of Washington)
- NGS testing on patient's blood (Karius)

These studies further identified the organism as microsporidia spp. ***Encephalitozoon cuniculi***

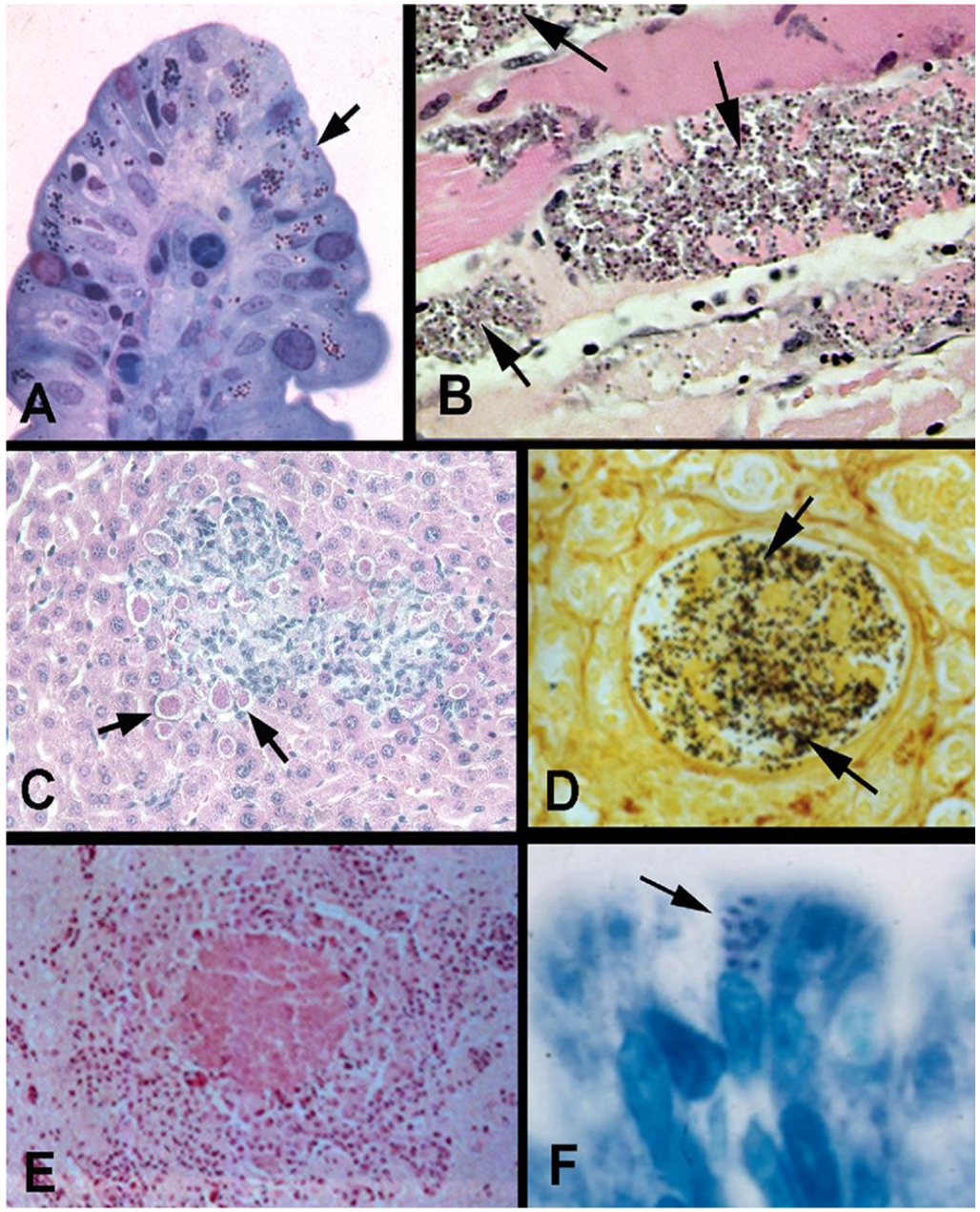
Microsporidia

- Obligate intracellular pathogen, closely related to fungi

  - Ovoid shaped (1-4 um) organisms
  - Can be seen on H&E
  - **Best highlighted by special stains:**
    - > Gram (Gram Positive)
    - > Modified Trichrome (Ryan-Blue)
    - > Calcofluor white (Fluorescent)

- Classically, associated with GI infection/diarrheal illness

- Can cause disseminated disease and affect virtually any organ system



Han et al. 2021 (PMID: 34190570)

Encephalitozoon cuniculi

- Well-known cause of renal, ocular, and neurologic disease in rabbits – “Granulomatous meningoencephalitis”

- However, it can also infect other mammals including **humans** and some species of birds

- Associated with disseminated disease (HIV/AIDS and transplant recipients)

- Cases of donor-derived infection affecting multiple organ recipients have been reported

    - Initial symptoms: fever of unknown origin and vague neuro/psychiatric symptoms

Mathis et al. 2005 (PMID: 16020683)

Tosoni et al. 2002 (PMID: 12011264)

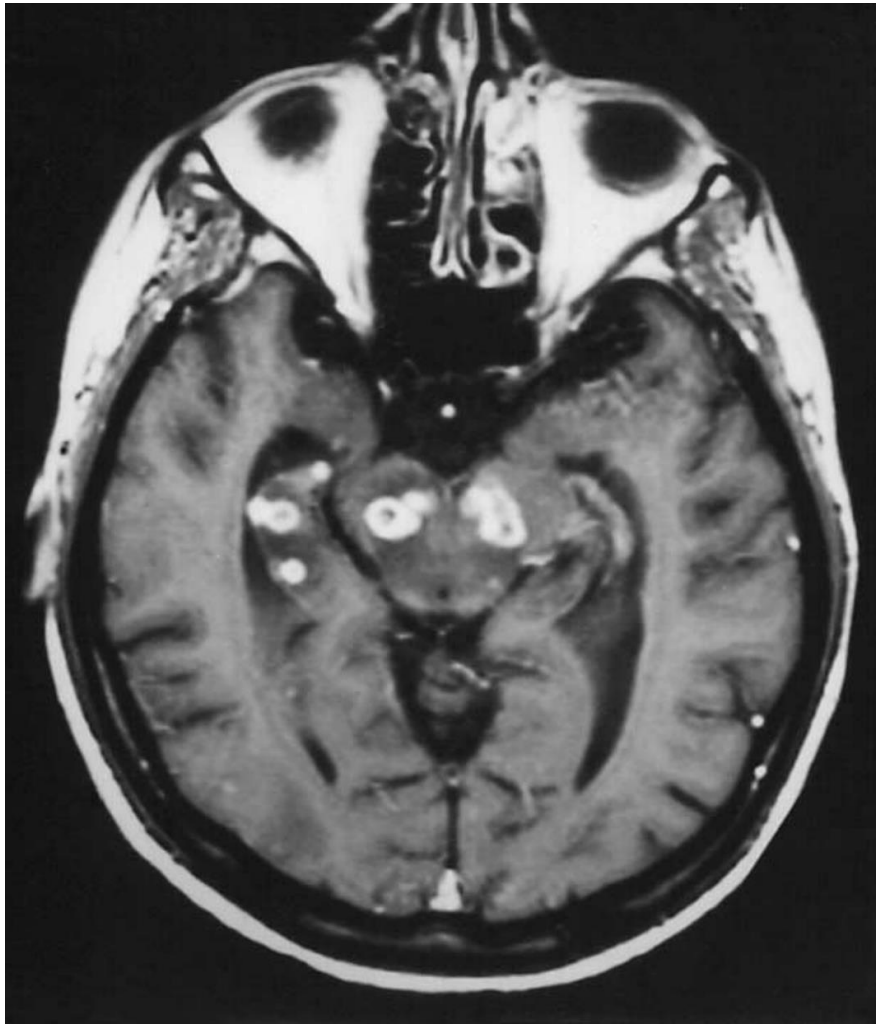
Radiographic findings in CNS *E. cuniculi* Infection

- Variable findings on imaging:

  <u>MRI imaging:</u> Small contrast enhancing/ring enhancing lesions with mild edema

  <u>CT imaging:</u> Multiple hypodense lesions

- Sometimes, however, there are no discrete lesions seen on imaging



Weber et al. 1997 (PMID: 9017940)

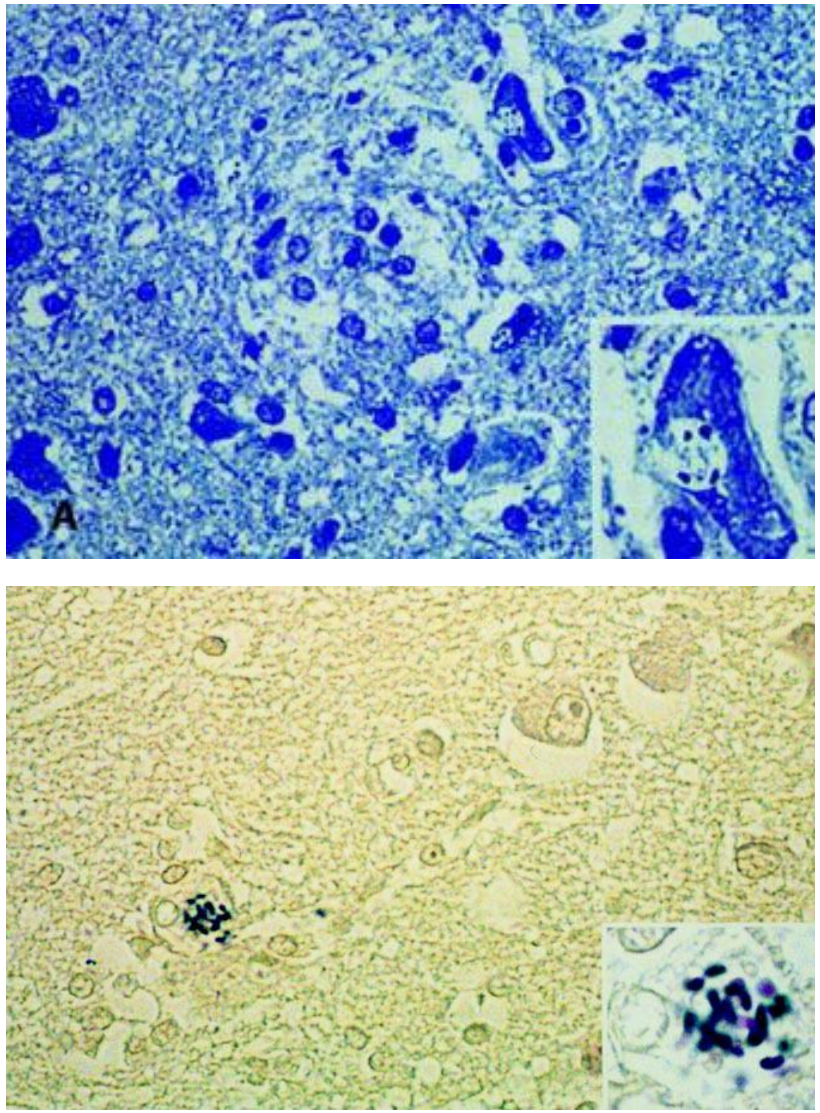
Neuropathologic findings in CNS Infection by *E. cuniculi*

Like in our case, previously published reports describing *E. cuniculi* CNS infection show:

1.) Organisms present in glial cells, macrophages, endothelial cells, and small vessel lumens

2.) Diffuse microglial nodules

3.) Leptomeningeal involvement and perivascular inflammation



Tosoni et al. 2002 (PMID: 12011264)

References

1. Han B, Pan G, Weiss LM. Microsporidiosis in Humans. Clin Microbiol Rev. 2021 Dec 15;34(4):e0001020. doi: 10.1128/CMR.00010-20. Epub 2021 Jun 30. PMID: 34190570; PMCID: PMC8404701.

2. Tosoni A, Nebuloni M, Ferri A, Bonetto S, Antinori S, Scaglia M, Xiao L, Moura H, Visvesvara GS, Vago L, Costanzi G. Disseminated microsporidiosis caused by Encephalitozoon cuniculi III (dog type) in an Italian AIDS patient: a retrospective study. Mod Pathol. 2002 May;15(5):577-83. doi: 10.1038/modpathol.3880566. PMID: 12011264.

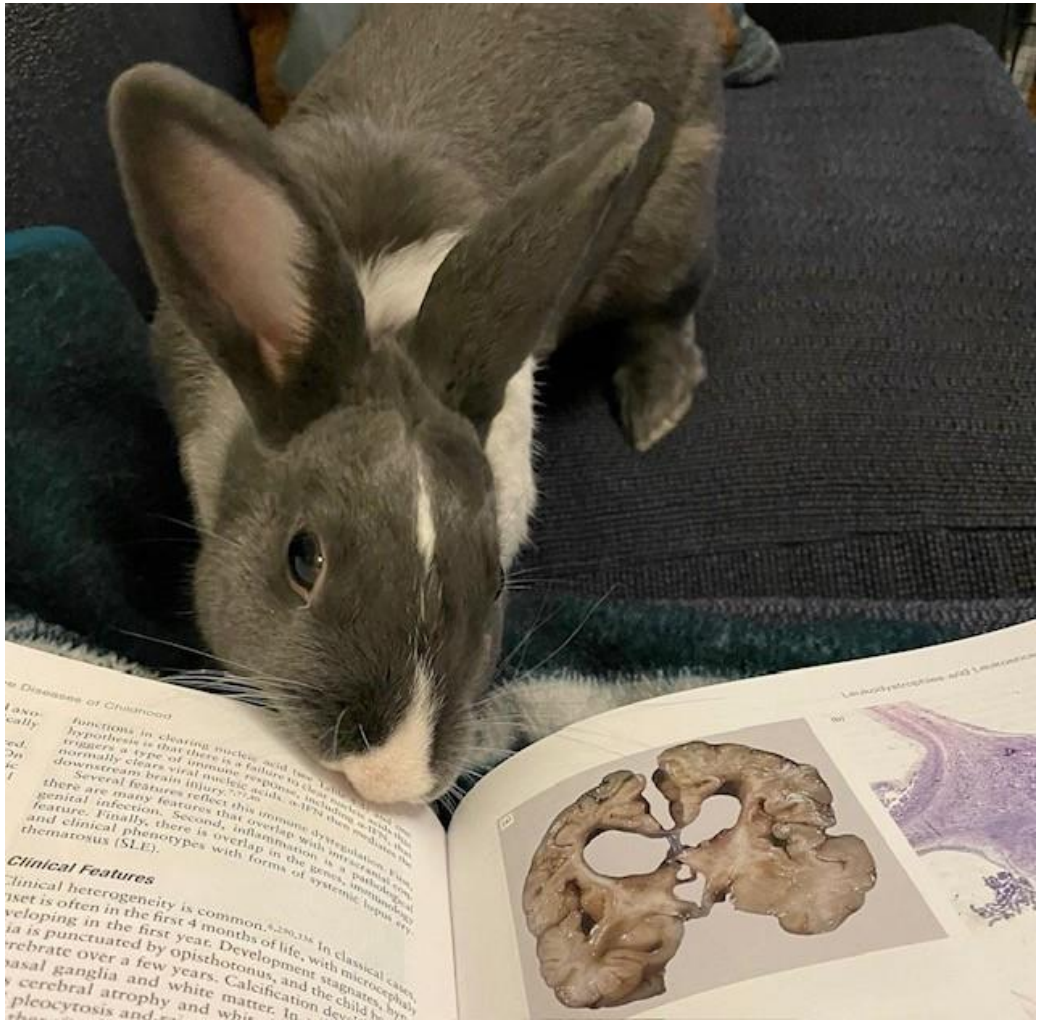
3. Mertens RB, Didier ES, Fishbein MC, Bertucci DC, Rogers LB, Orenstein JM. Encephalitozoon cuniculi microsporidiosis: infection of the brain, heart, kidneys, trachea, adrenal glands, and urinary bladder in a patient with AIDS. Mod Pathol. 1997 Jan;10(1):68-77. PMID: 9021729.

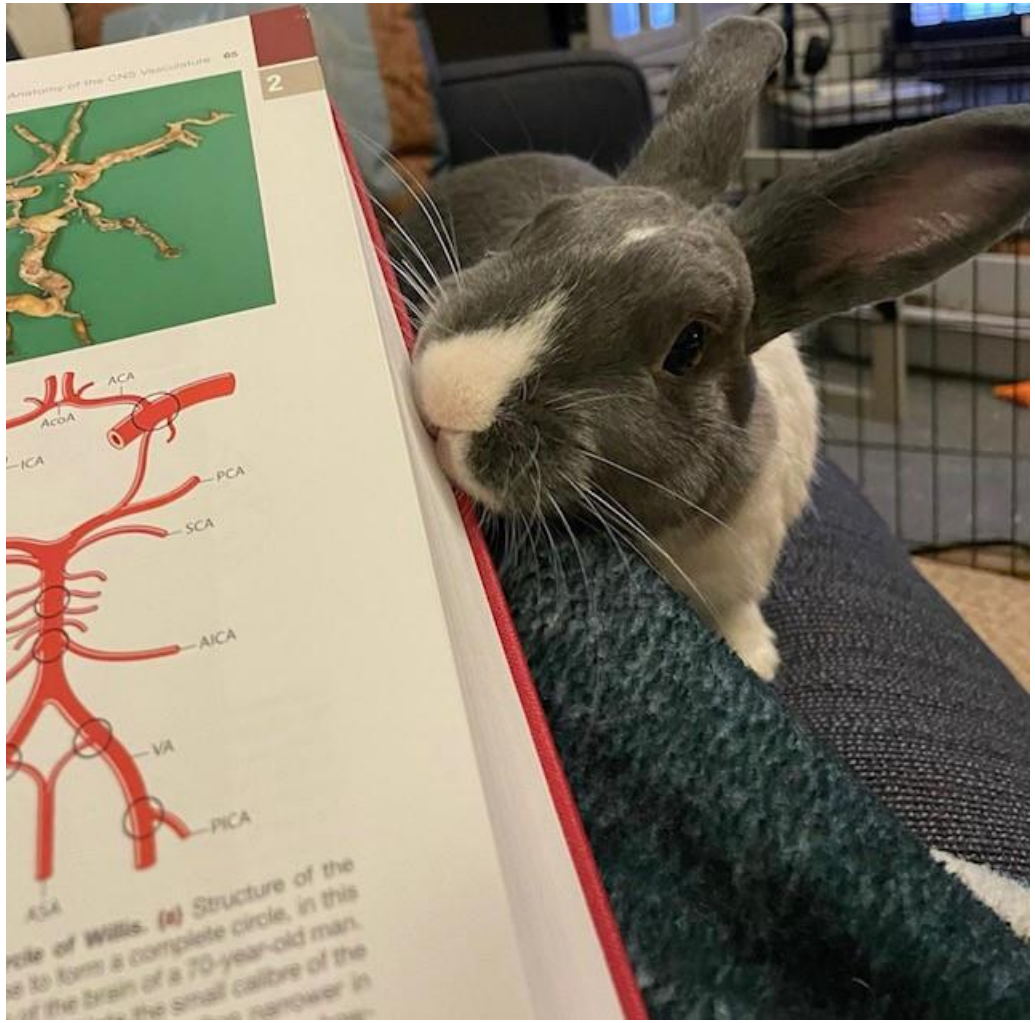
4. Smith RM, Muehlenbachs A, Schaenmann J, Baxi S, Koo S, Blau D, Chin-Hong P, Thorner AR, Kuehnert MJ, Wheeler K, Liakos A, Jackson JW, Benedict T, da Silva AJ, Ritter JM, Rollin D, Metcalfe M, Goldsmith CS, Visvesvara GS, Basavaraju SV, Zaki S. Three Cases of Neurologic Syndrome Caused by Donor-Derived Microsporidiosis. Emerg Infect Dis. 2017 Mar;23(3):387-395. doi: 10.3201/eid2303.161580. PMID: 28220747; PMCID: PMC5382757.

5. Weber R, Deplazes P, Flepp M, Mathis A, Baumann R, Sauer B, Kuster H, Lüthy R. Cerebral microsporidiosis due to Encephalitozoon cuniculi in a patient with human immunodeficiency virus infection. N Engl J Med. 1997 Feb 13;336(7):474-8. doi: 10.1056/NEJM199702133360704. PMID: 9017940.

6. Mathis A, Weber R, Deplazes P. Zoonotic potential of the microsporidia. Clin Microbiol Rev. 2005 Jul;18(3):423-45. doi: 10.1128/CMR.18.3.423-445.2005. PMID: 16020683; PMCID: PMC1195965.

Thank you!





"Teepah", Pictures courtesy of Dr. Maria Gubbiotti (MD Anderson)

Extra Slides

CNS / Infectious disease work up in addition to cultures (Negative)

	Organism	Methodology	Result
Bacterial	*Escherichia coli K1*	PCR (CSF)	**Negative**
	Haemophilus influenzae	PCR (CSF)	**Negative**
	Listeria monocytogenes	PCR (CSF)	**Negative**
	Neisseria meningitidis	PCR (CSF)	**Negative**
	Streptococcus agalactiae	PCR (CSF)	**Negative**
	Streptococcus pneumoniae	PCR (CSF)	**Negative**
	Treponema pallidum	Serology, VLDR (CSF)	**Negative**
	Rickettsia spp.	Serology (Serum)	**Negative**
Viral	*HSV1/HSV2/VZV/HHV6*	PCR (CSF)	**Negative**
	Enterovirus	PCR (CSF)	**Negative**
	Human Parechovirus	PCR (CSF)	**Negative**
	West Nile Virus (WNV)	PCR/Serology (CSF)	**Negative**
	JC Virus	PCR (CSF)	**Negative**
Fungal/ Parasite	*Cryptococcus neoformans/gattii*	PCR (CSF)/Serology (CSF)	**Negative**
	Histoplasma capsulatum	Serology (Serum)	**Negative**
	Toxoplasma gondi	Serology (Serum)	**Negative**
	Coccidoides immitis	Serology (Serum)	**Negative**
	Leshmania spp.	Serology (Serum)	**Negative**
	Invasive Fungal Disease	Fungitell and Galactomanin	**Negative**