“Vascular Neuropathology: The Road Less Traveled”

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Disclosures

- I have no relevant financial relationships to disclose
- I sincerely wish I did

Learning Objectives

- Summarize common topics in vascular neuropathology
- Discuss uncommon clinical and pathologic characteristics associated with some common vascular neuropathology lesions
- Identify the clinical and pathologic features associated with selected rare vascular neuropathology diagnoses

Vascular neuropathology

- All adult neuropathologists are going to see vascular disease (particularly in the autopsy realm)
- Even pediatric neuropathologists may see some vascular disease like vascular malformations

Vascular neuropathology: classic topics

- Anatomy of the circle of Willis
- Vascular territories in the brain
- Risk factors for vascular disease
- Large-vessel (atherosclerosis) vs. small-vessel (arteriolosclerosis) disease
- Etiology of infarcts: thrombosis vs. embolism
- Etiology of hemorrhages: intracerebral vs. subarachnoid

Vascular neuropathology: classic topics

- Morphology and evolution of infarcts: acute, subacute, and chronic (liquefactive necrosis)
- Morphology and pathophysiology of ischemia
- Vascular malformations
  - Arteriovenous malformation (AVM)
  - Cavernous angioma/hemangioma (“cavernoma”)
  - Venous angioma
  - Capillary telangiectasia
- Aneurysms: saccular, fusiform, and mycotic

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Vascular neuropathology: classic topics

- Vasculitis
  - Giant-cell arteritis
  - Primary CNS angiitis/vasculitis
  - Polyarteritis nodosa
- Inherited disorders (e.g., CADASIL)
- Cerebral amyloid angiopathy
- Vascular dementia

Vascular neuropathology: classic topics

- An audience of neuropathologists will be familiar with most, if not all, of these topics
- Neuropathologists teach these topics to medical students, rotating residents, and neuropathology fellows
- Neuropathology fellows likely lecture on these topics as well

Overview of this presentation

- Five clinical cases
- Purpose in each case is to demonstrate one of the following:
  - Classic lesion with an interesting pathologic twist
  - Classic pathology with an interesting clinical twist
  - Classic pathology with a rare etiology
  - Classic, rare topics
- I’ve only seen each type of case once or very rarely

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CASE #1

Prior history

- Initially presented in October 2007 as a 10-year-old boy with right basal ganglia AVM rupture causing a generalized tonic-clonic seizure and coma
- Hospitalized for a “long time” and required surgery, embolization, extraventricular drain placement, and treatment of CSF infection
- Received gamma knife treatment to residual AVM in 2008
- Saw neurology as outpatient initially in May 2016; had improved with time and could walk and talk but with residual left hemiparesis
- Got Botox every six months for leg and arm spasticity
- Also had dysarthria and cognitive/behavioral sequelae

Prior history

- Began to have breakthrough seizures after being weaned off some antiepileptic drugs he was on following the AVM rupture
- Majority of outpatient visits were to titrate epilepsy medications for breakthrough seizures and manage urinary incontinence
- 2020: presented with worsening seizures and subacute blood products on MRI at site of AVM concerning for re-rupture with increasing hydrocephalus; differential included giant cavernous angioma with repeat acute bleeding vs. very slow evolution of prior bleed; right-sided VP shunt placed; shunt revised 11/2022
- Has had multiple falls and fractures over time

Prior history

- Multiple presentations and admissions to the hospital
  - Headaches
  - Seizures
  - Hydrocephalus (including high-volume shunt tap in 6/2022)
  - Shunt infection causing constipation and ventriculitis; reimplanted on left side
  - Urinary incontinence
  - Possible colitis (2/2023)
  - Fractures

Final admission

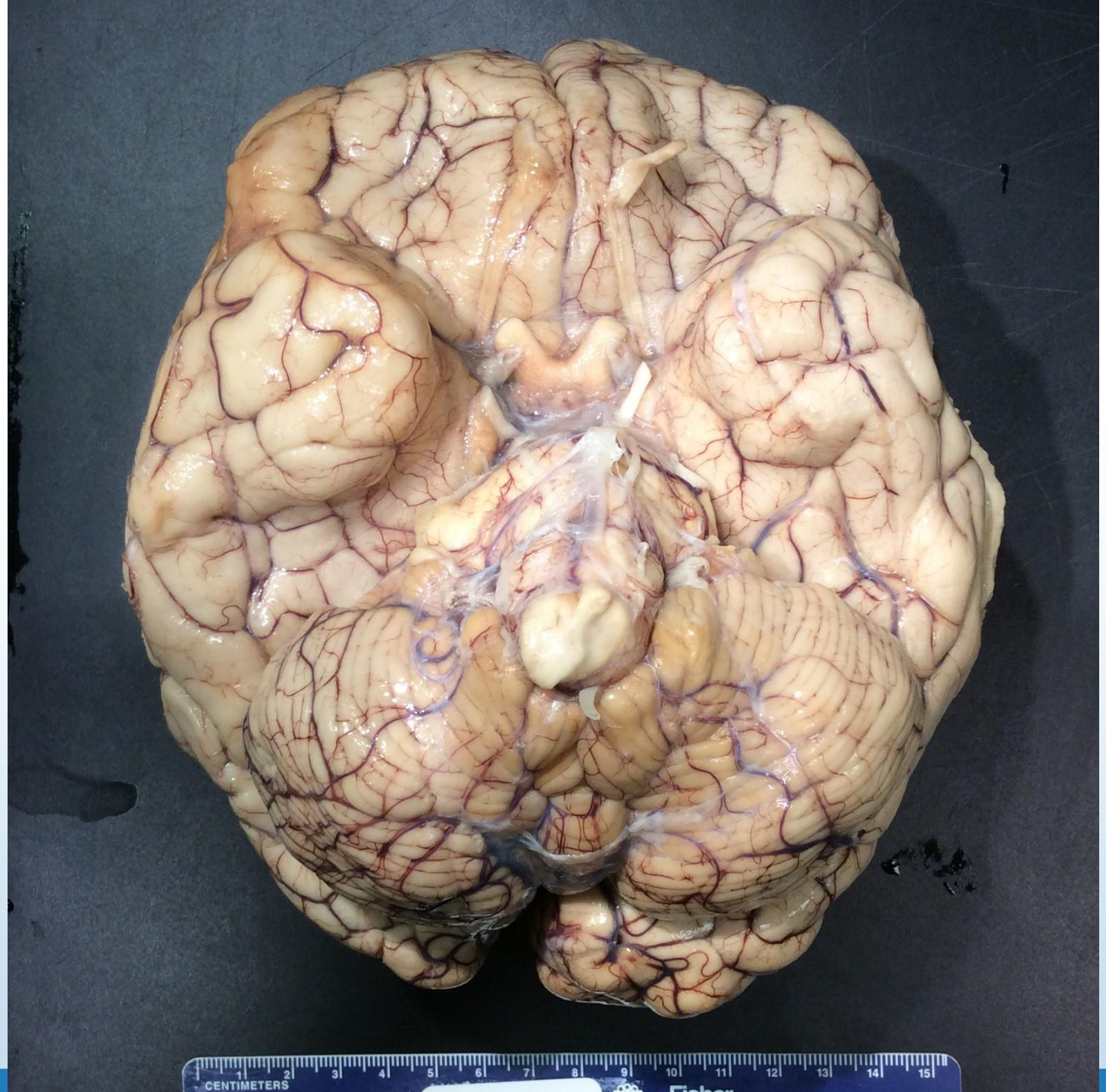
- Presented to hospital (now age 26) on 4/7/2023 with increased headaches, right-sided head swelling, and increasingly unsteady gait
- Shunt tap 3/2023 grew *Cutibacterium acnes*; current tap negative; treated presumptively with IV penicillin
- EEG showed right hemispheric delta activity and right anterior quadrant sharp wave discharges
  - Generalized/multifocal encephalopathy
  - Structural abnormality with epileptogenic focus
  - No seizures observed

Final admission

- Head CT scan
  - Cerebellar tonsillar herniation; increased since 3/8/2023
  - Increasing cystic hypodensity extending posteriorly from the encapsulated hematoma and inferiorly, exerting mass effect upon the brainstem and cerebellum, contributing to increased herniation
  - Increased obstructive hydrocephalus since 1/24/2023
- 4/20/2023: complained of abdominal pain, vomiting, and continued headache; abdominal X-ray revealed possible kinking of shunt; baclofen added as needed; abdominal pain and nausea subsided after 4/21, but headaches continued

Final admission

- 4/24/2023: found suddenly unresponsive at 8:10 a.m.
  - No seizure per witness in room
  - In asystole; code called; CPR initiated; intubated
  - 40 cc of CSF easily aspirated from shunt valve
  - CPR continued for 55 minutes
  - Resuscitation efforts unsuccessful
  - Full autopsy requested; general autopsy unrevealing for cause of death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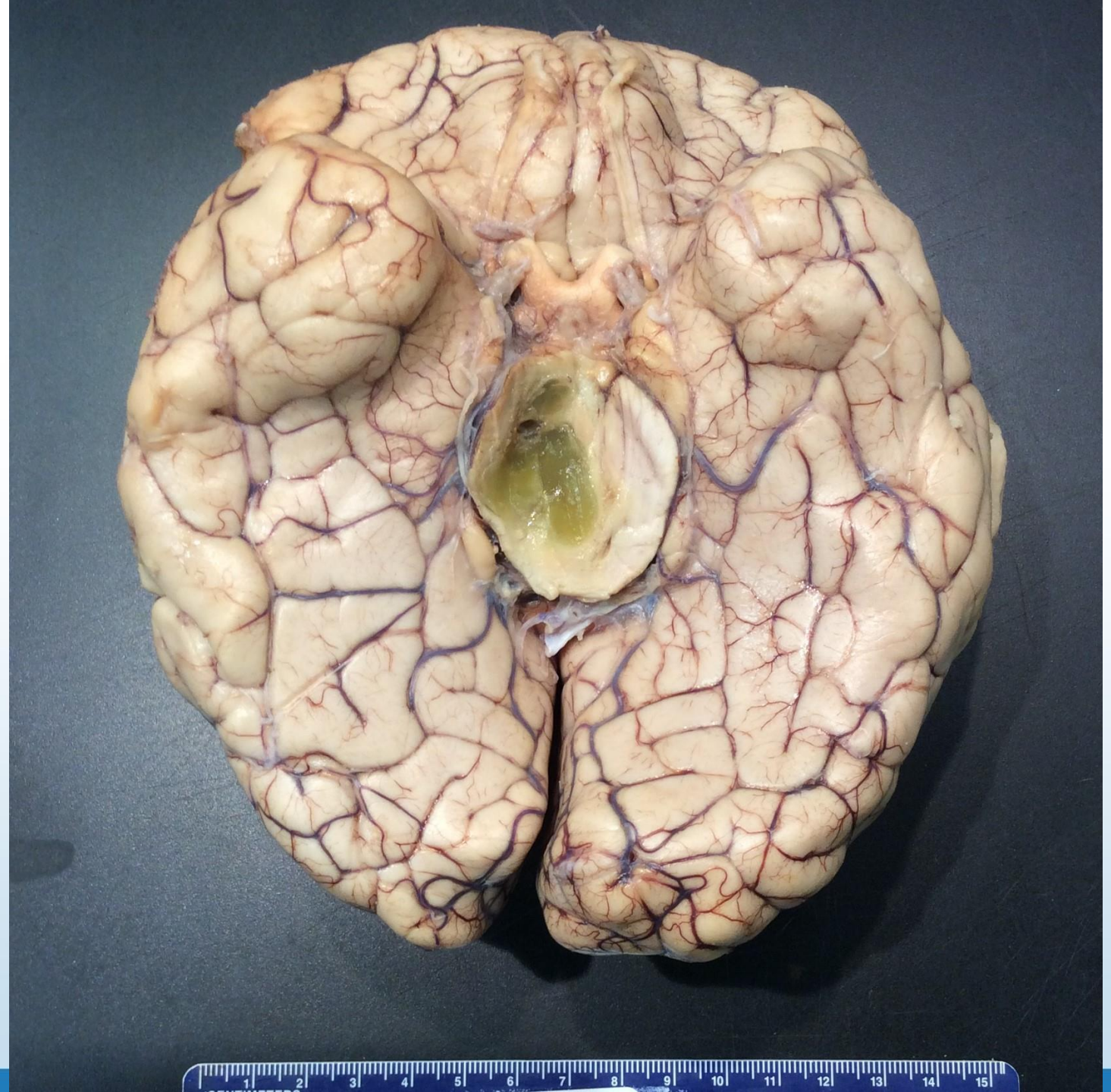

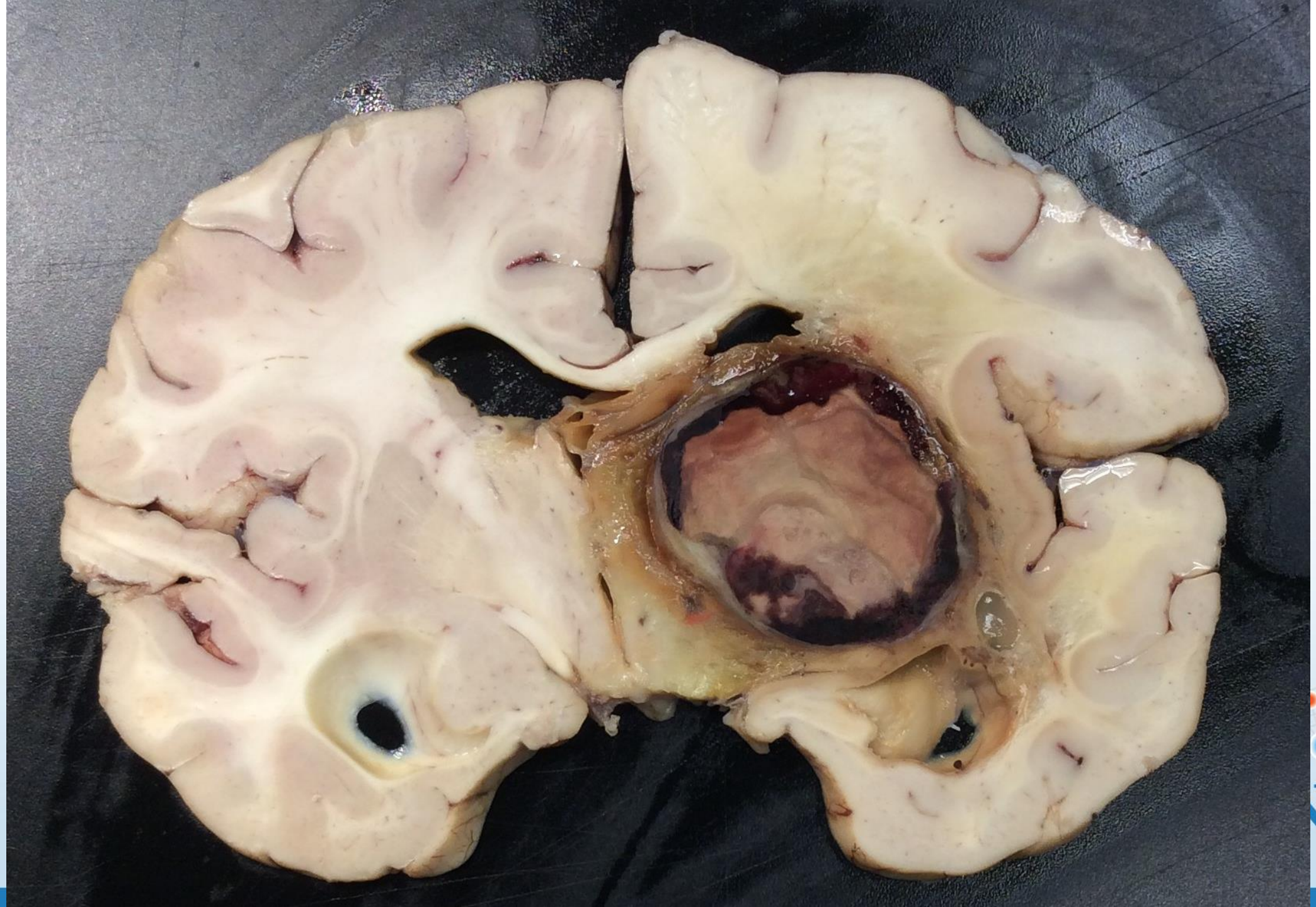

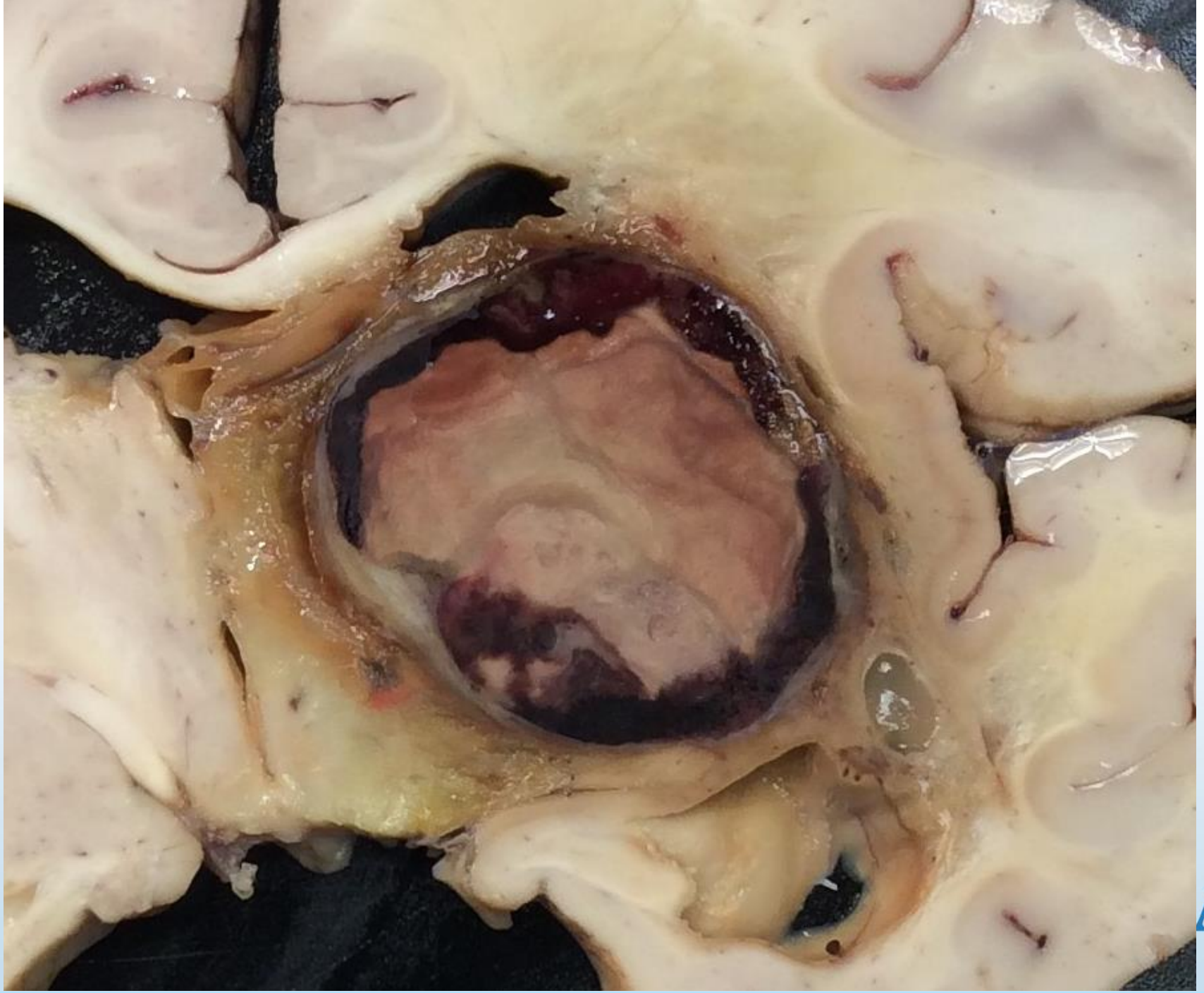

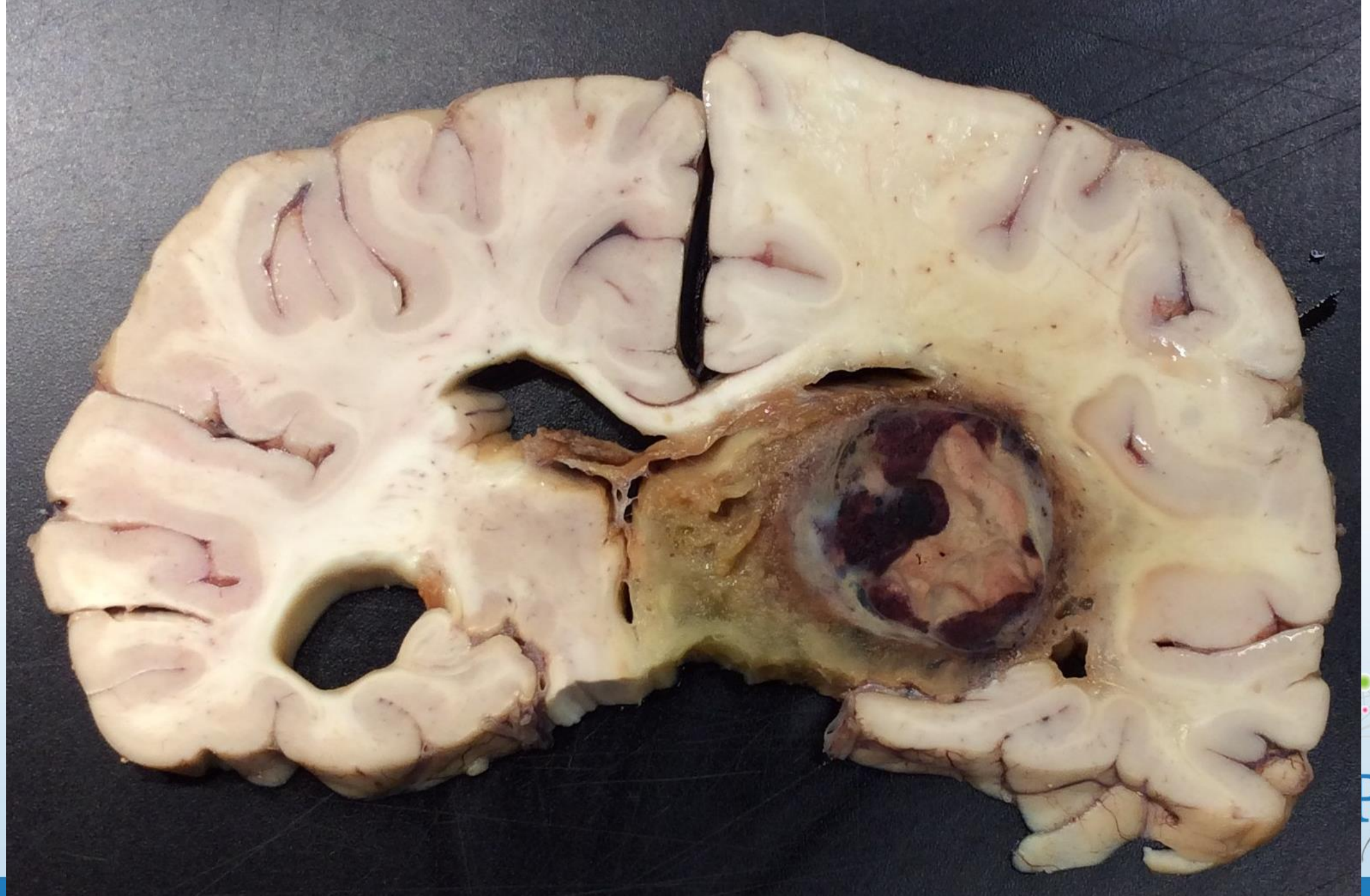

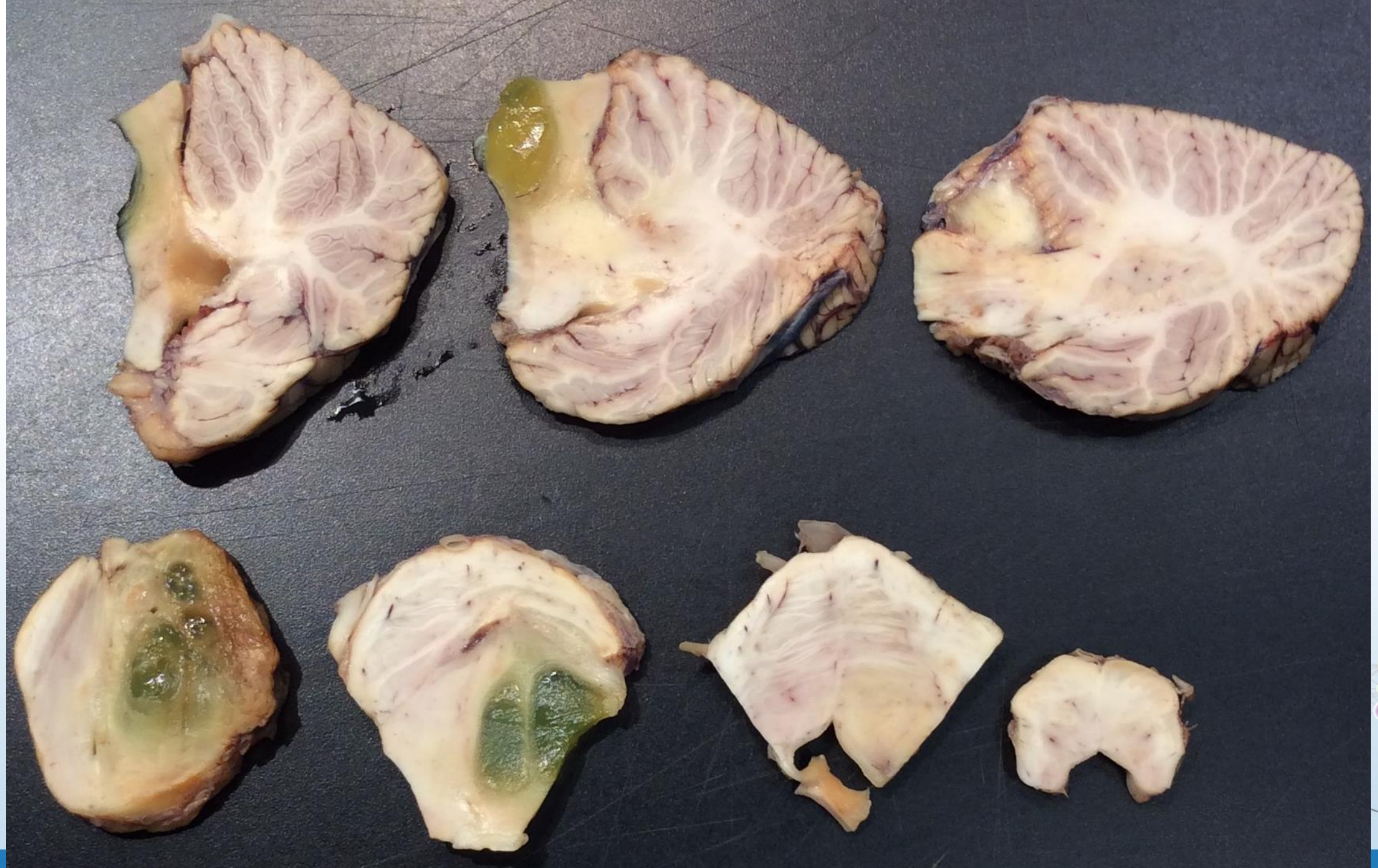

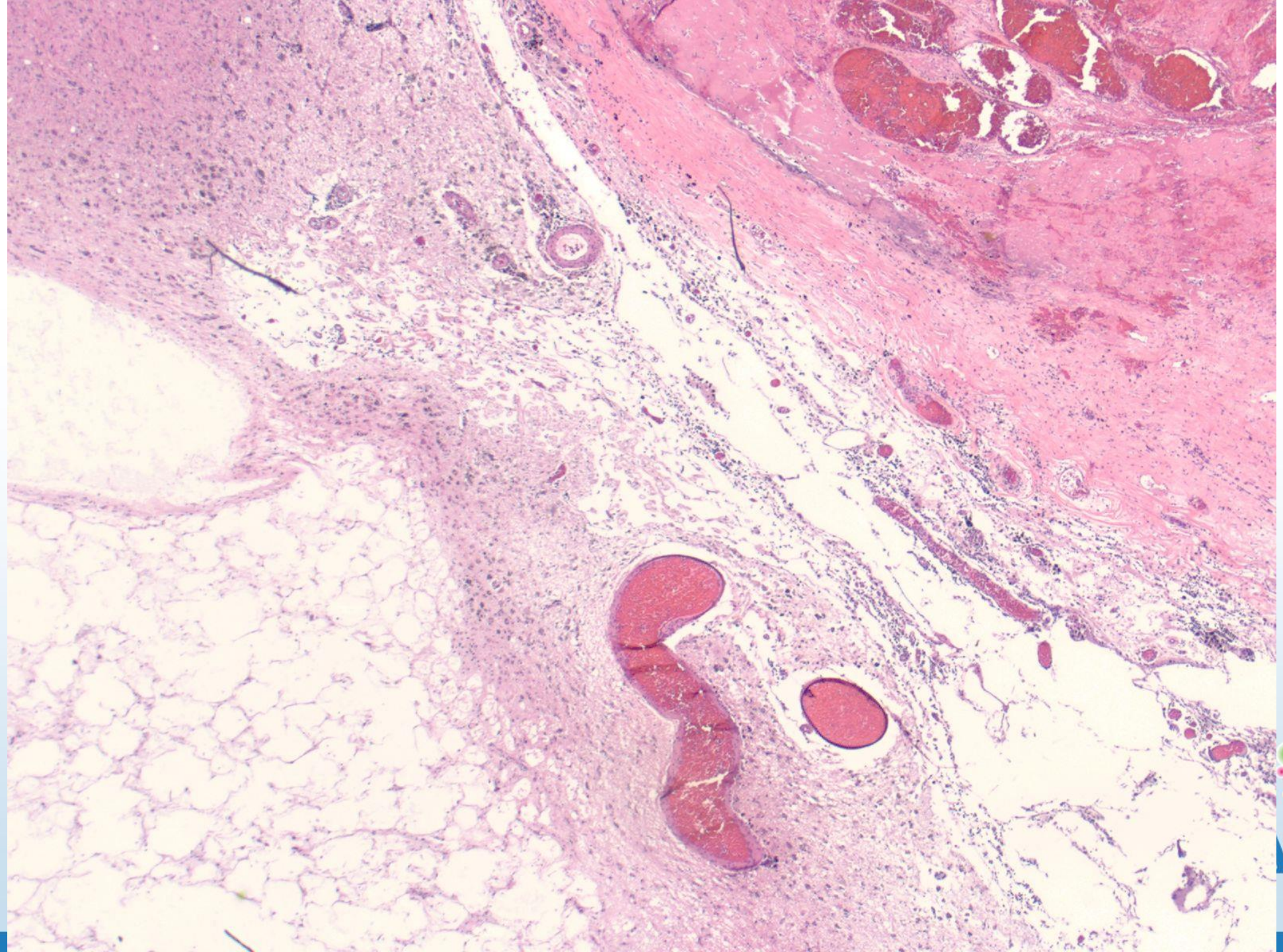

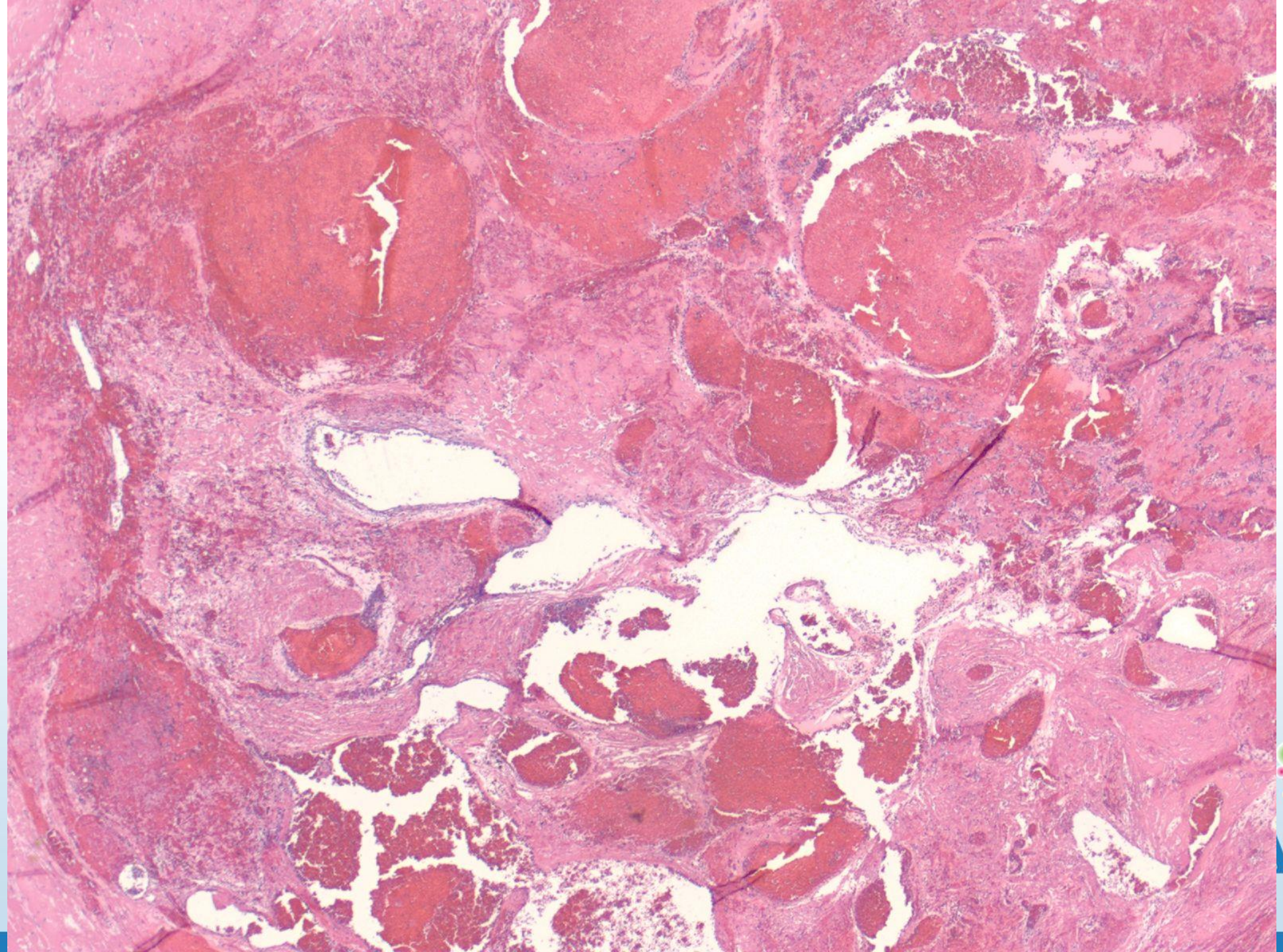

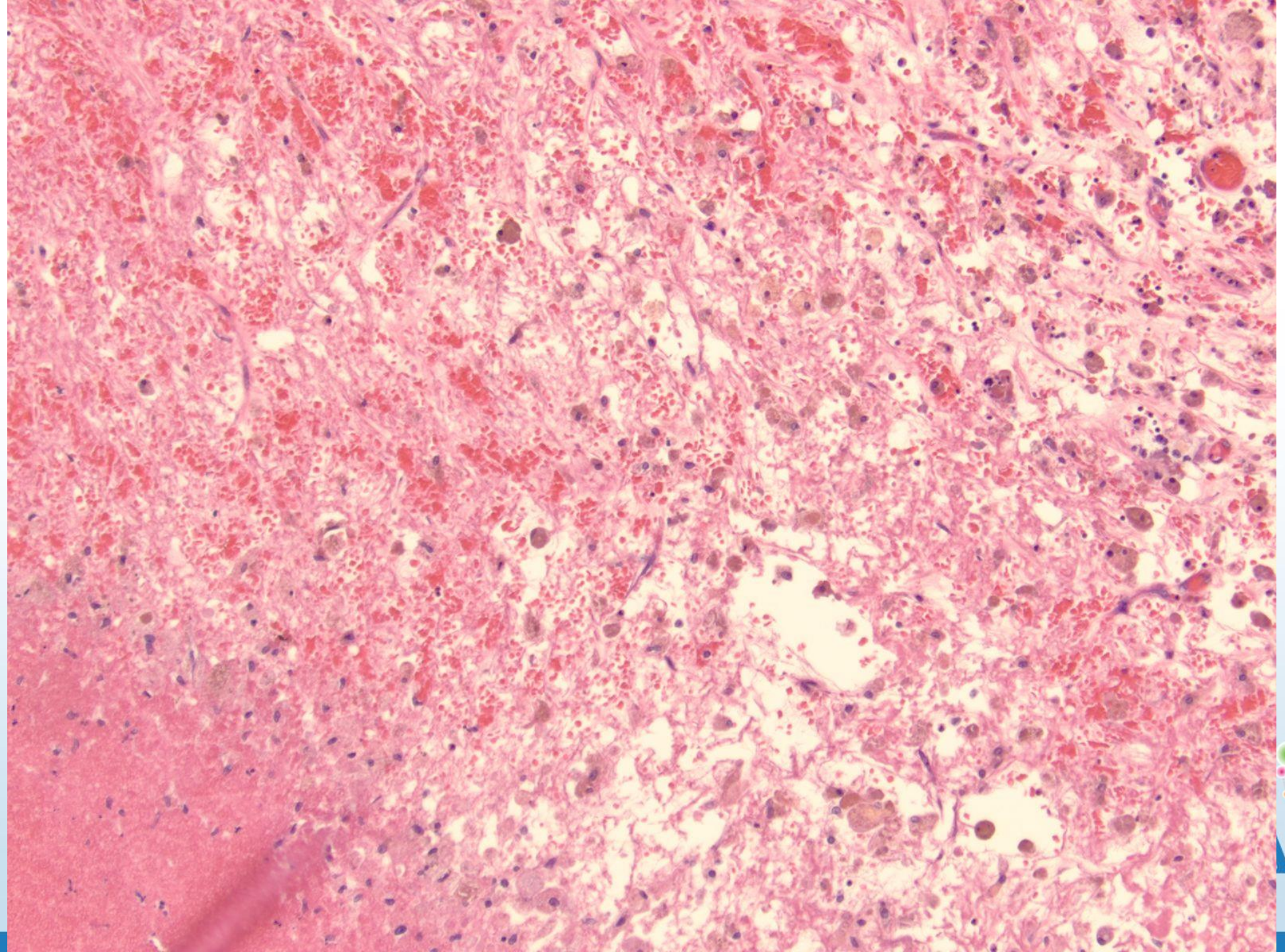

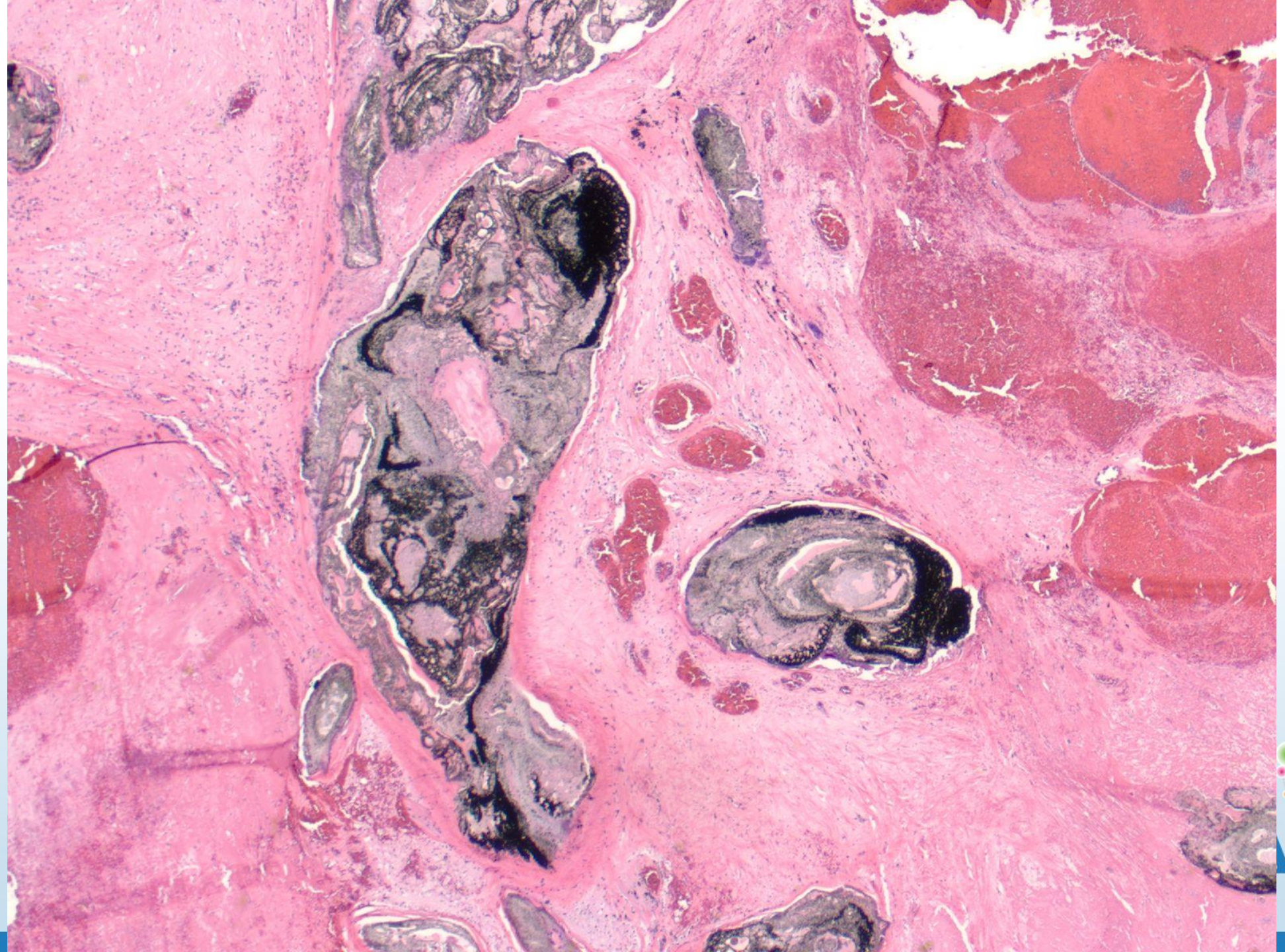

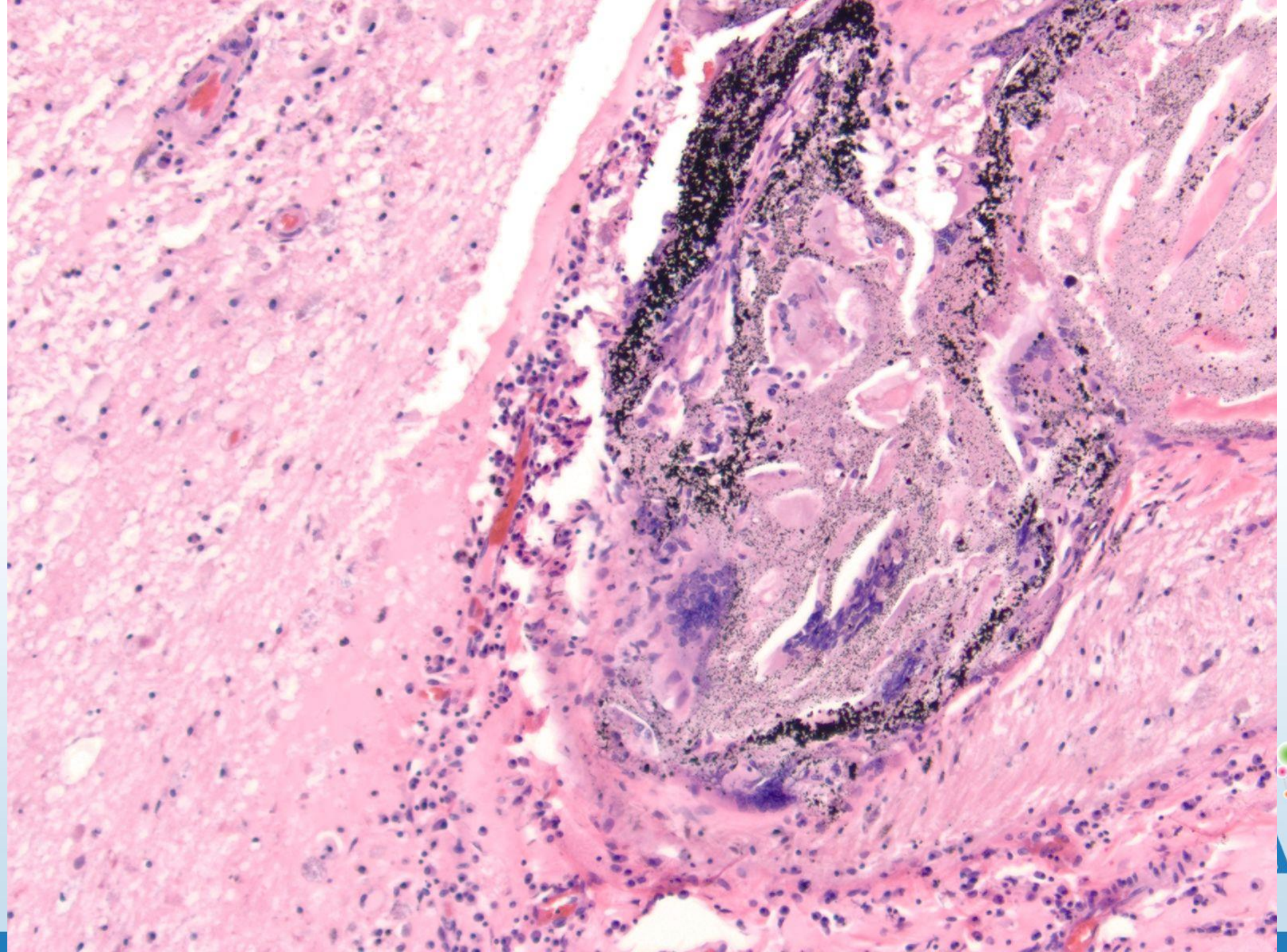

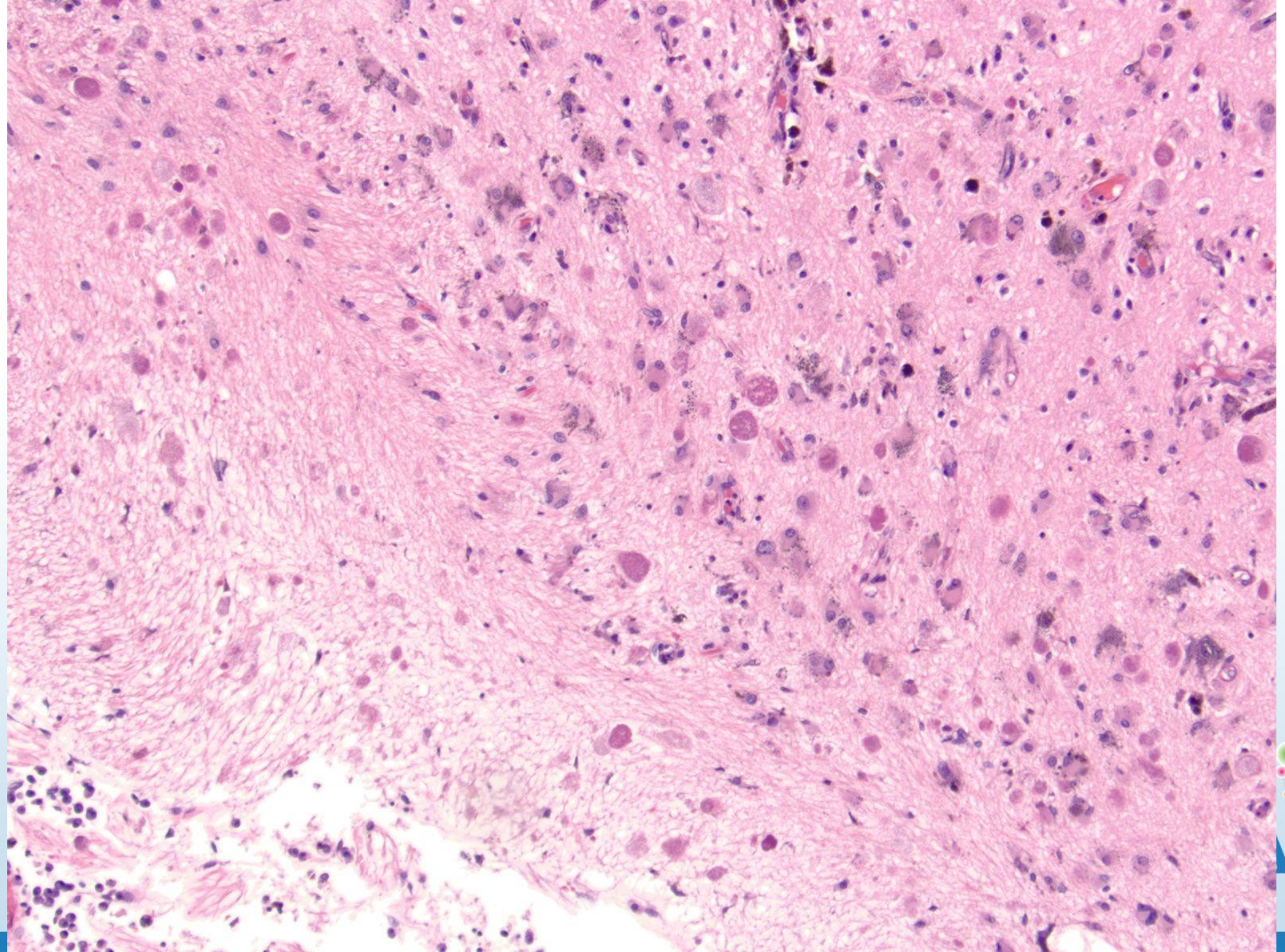

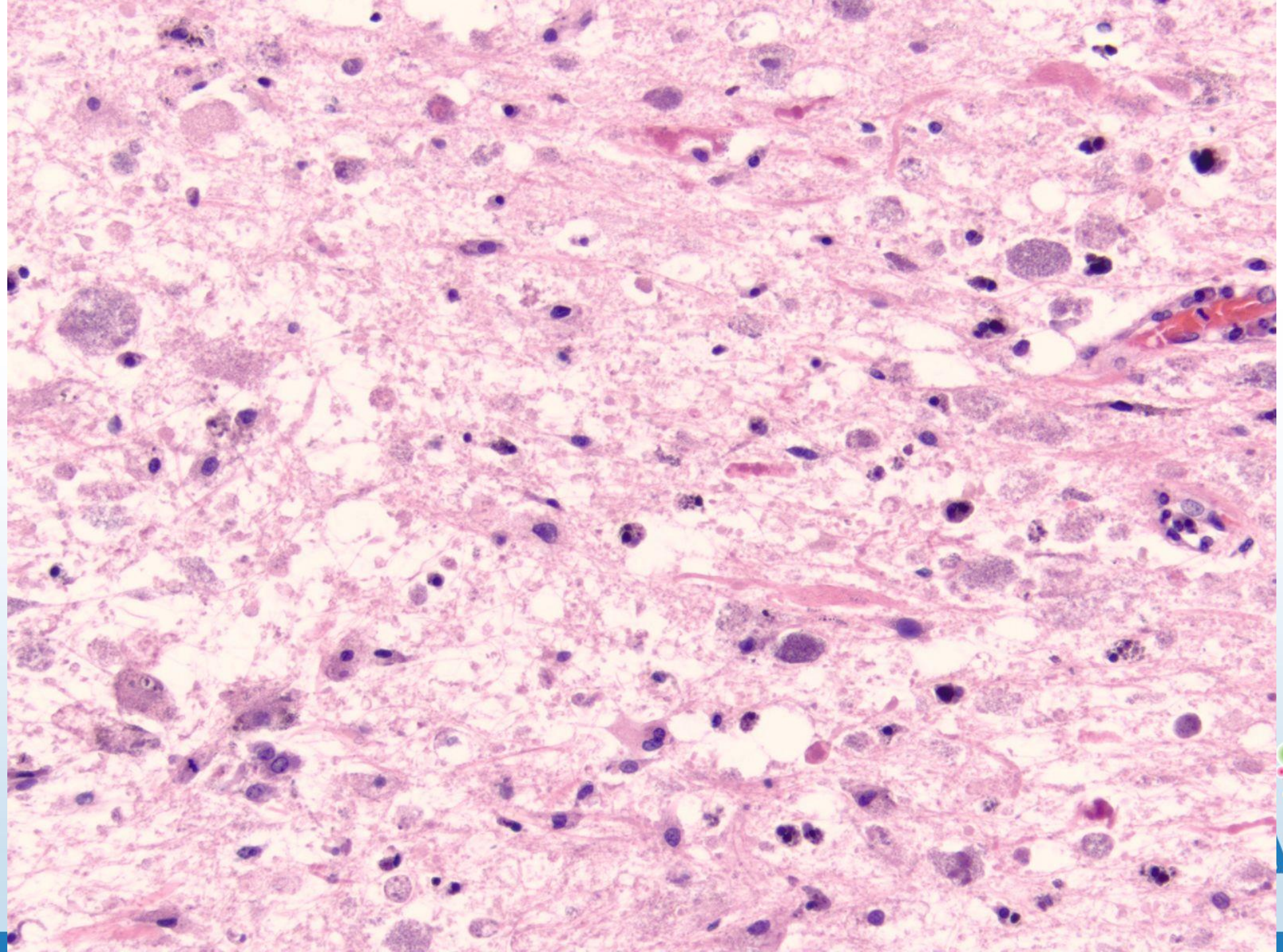

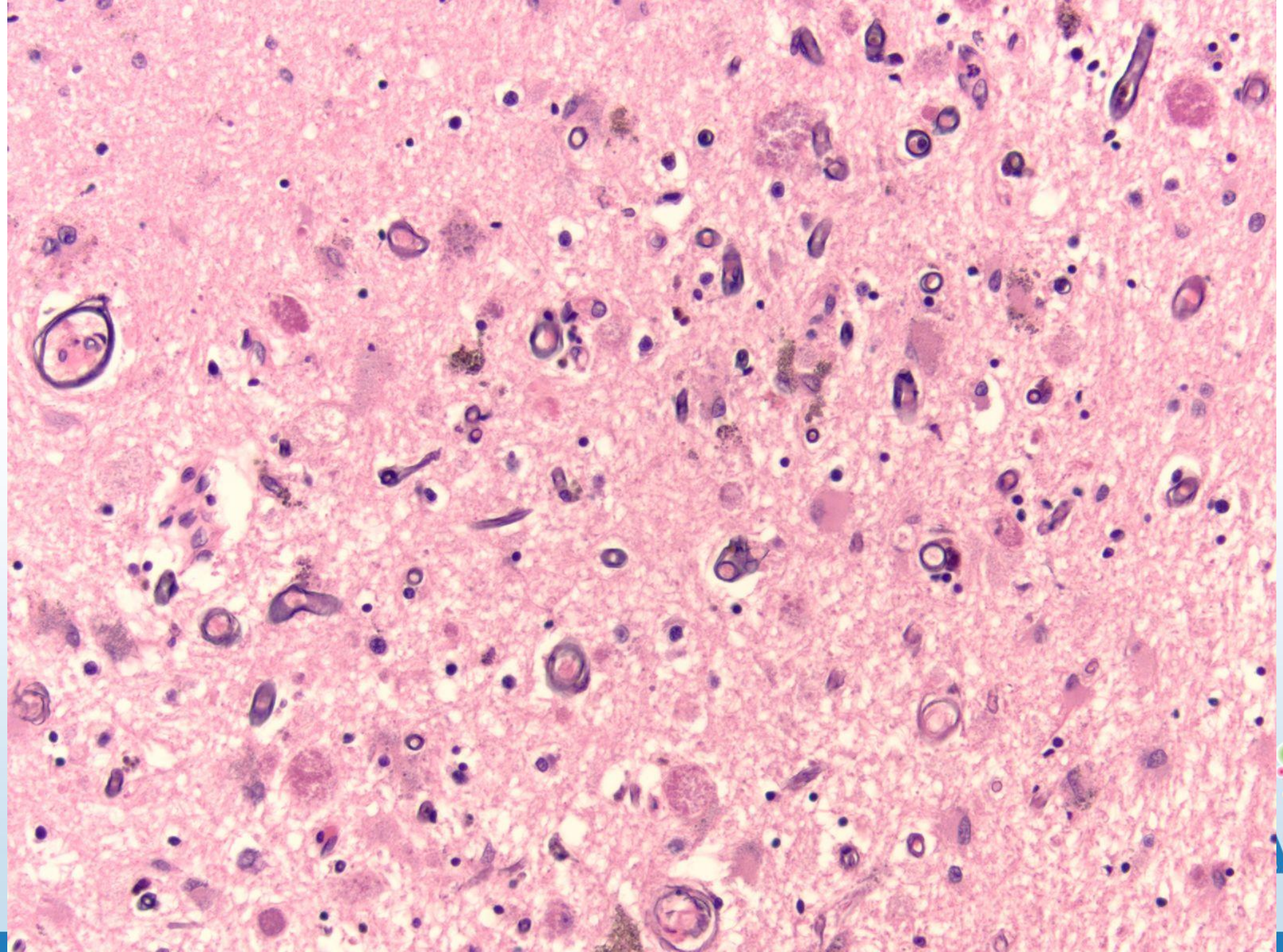

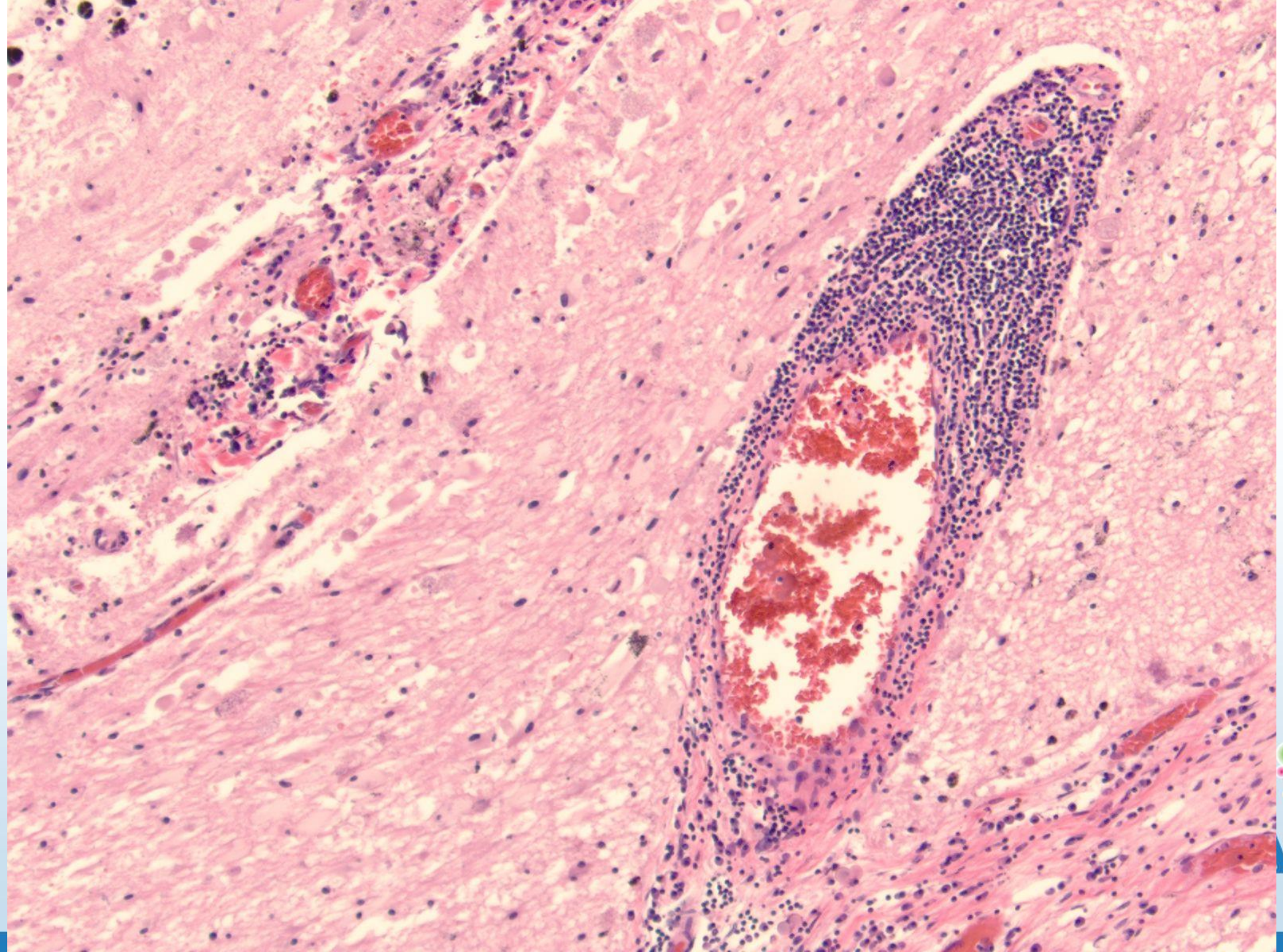

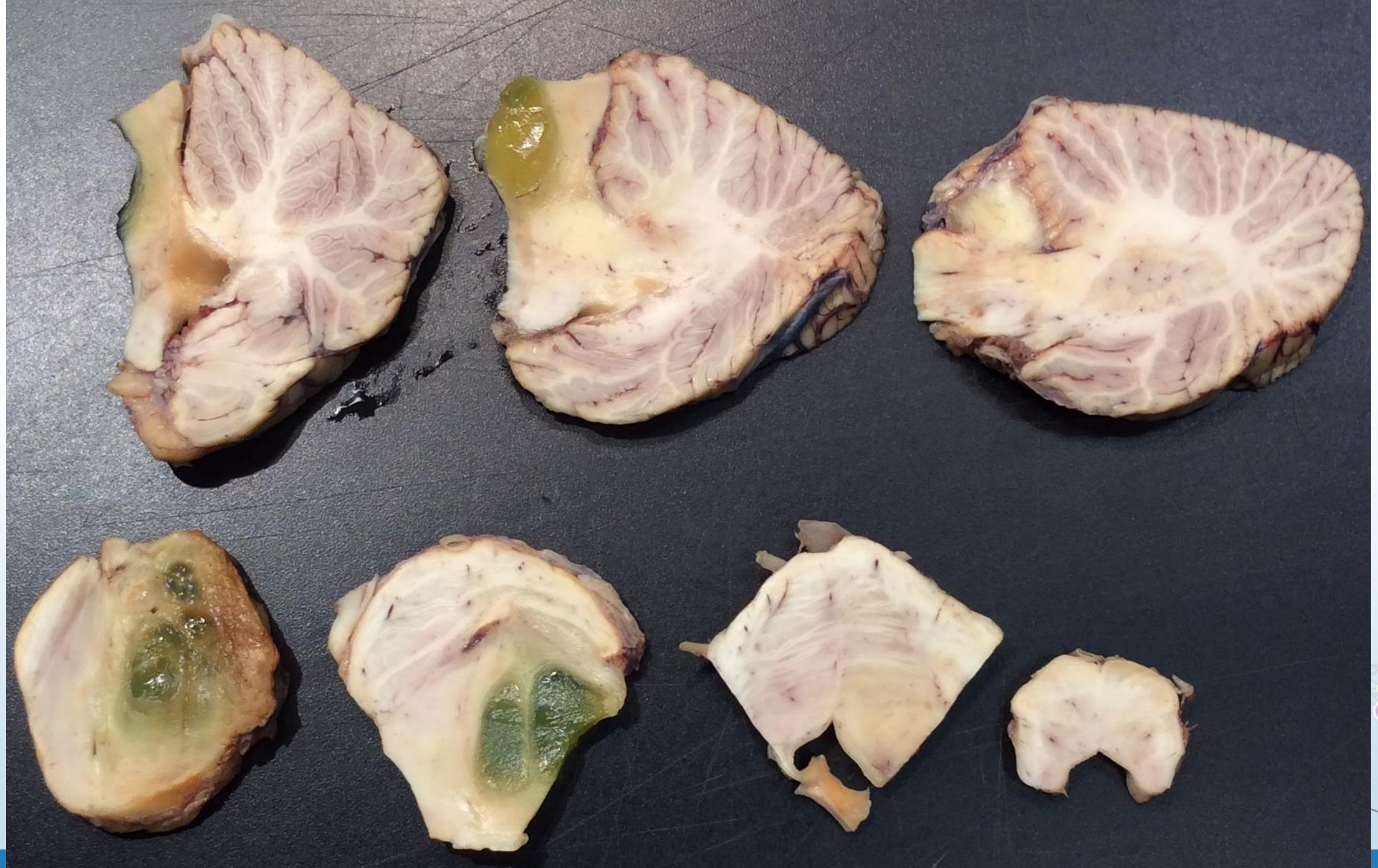

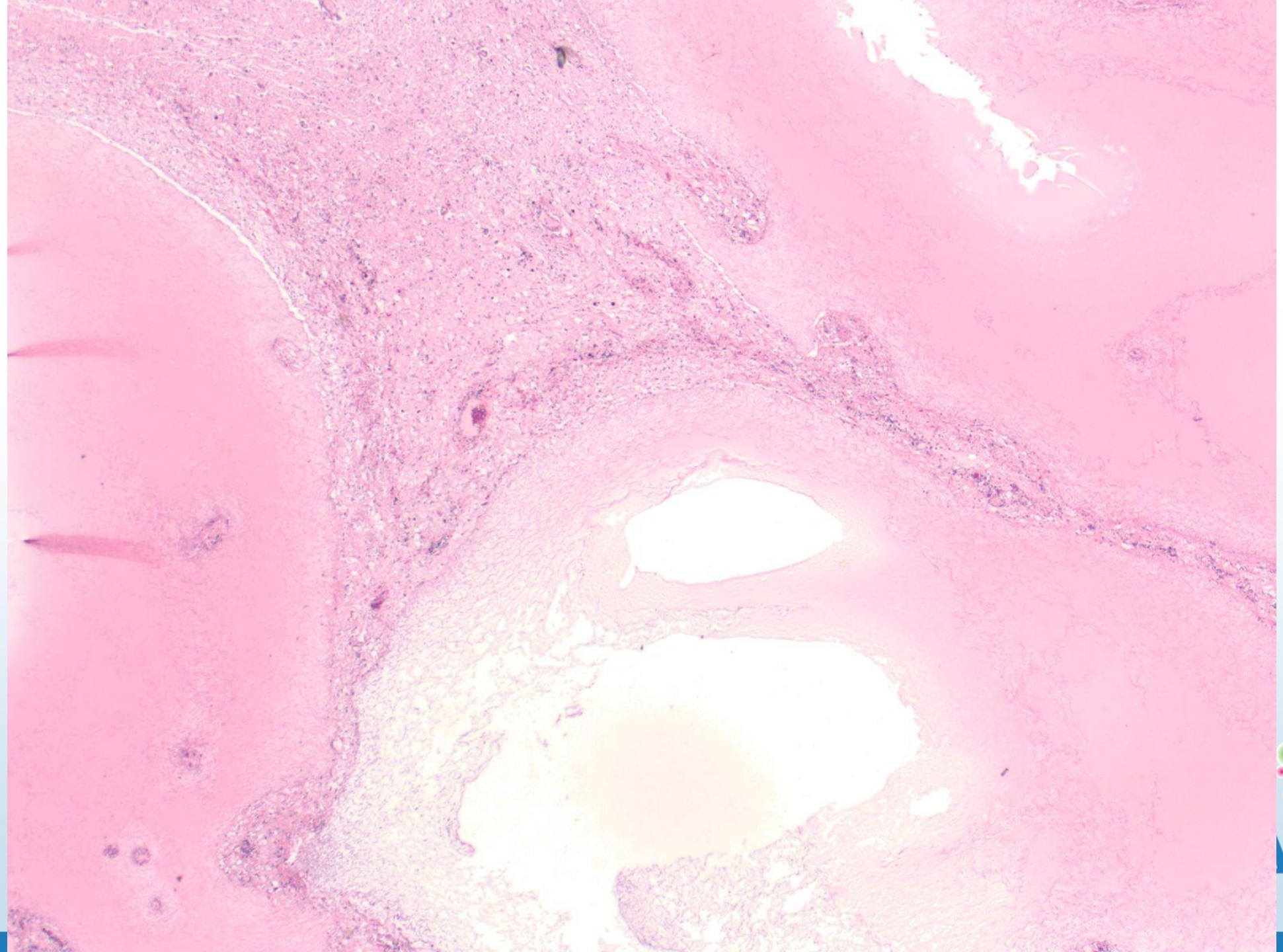

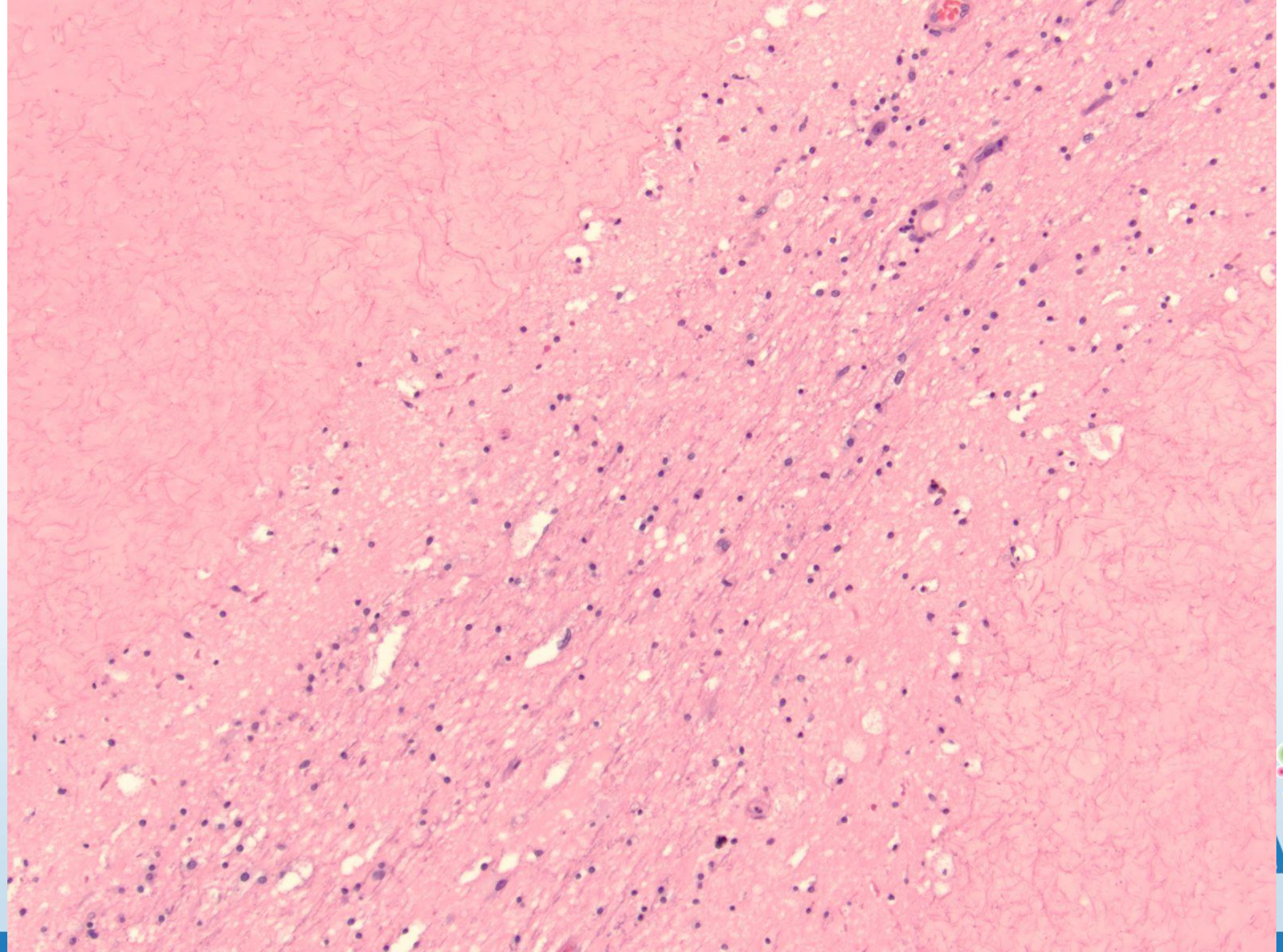

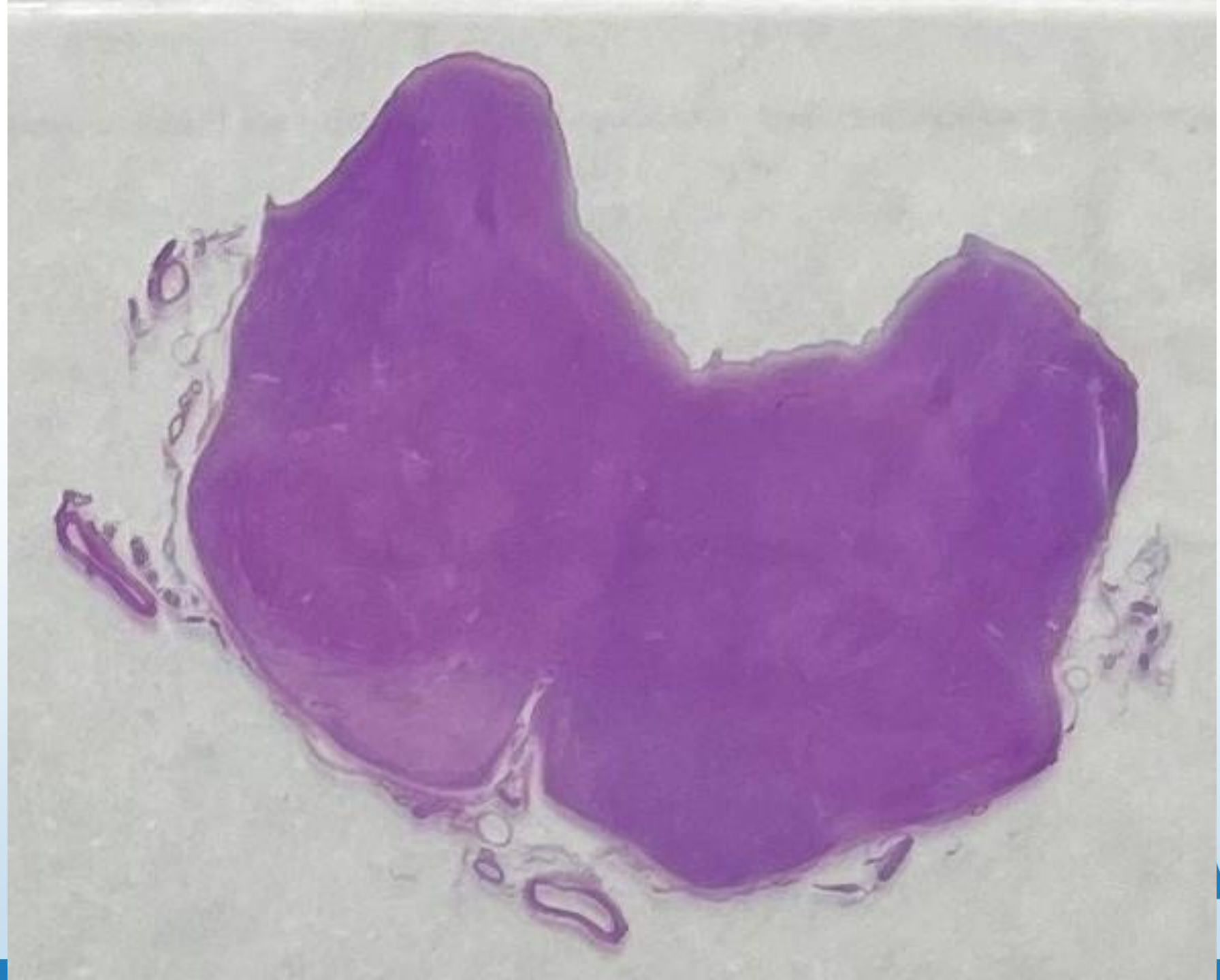

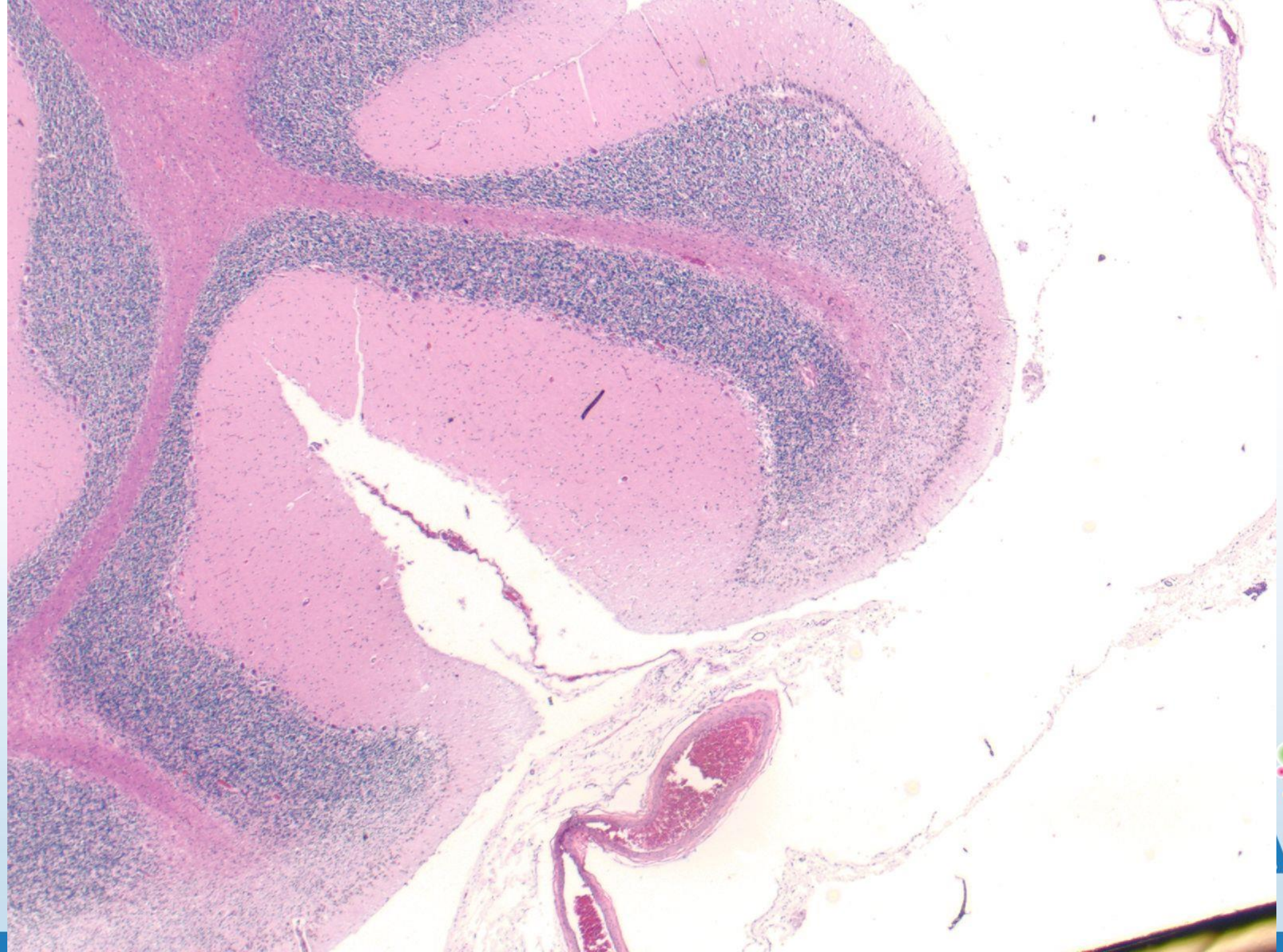

Final Neuropathologic Diagnosis

- Chronic encapsulated intracerebral hematoma, right basal ganglia
- Cystic degeneration, consistent with treatment sequelae of prior arteriovenous malformation
- Cerebellar tonsillar hernination
- Acute infarct, cerebellum
- Wallerian degeneration, right medullary pyramid

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Chronic encapsulated intracerebral hematoma

- First described in 1981
- Presents as a subtle, slow-growing lesion exerting mass effect
- Chronic, progressive development of intracranial hypertension may occur in most cases
- CT scan: blood in various phases of degradation
- MRI with gadolinium: peripheral contrast enhancement
- May simulate a neoplasm
- Most frequent cause: **AVM with rupture**
- Can represent a delayed complication after stereotactic radiosurgery

Scalia, *et al*, *Br J Neurosurg* 2022 Jan 8, 1-6

Chronic encapsulated intracerebral hematoma—pathophysiology

- Brain tissue creates a fibroblastic reaction to initial hemorrhage with formation of the initial capsule membrane
- Subsequent bleeding produces granulation tissue and promotes the fibroblastic reaction to form a fibrous capsule and expand hematoma
- With radiosurgery, repetitive minor bleeding with the radionecrotic brain tissue may start the formation of the encapsulated hematoma
- Radiosurgery may cause hypoxic stress and induce transcription of VEGF with abnormal angiogenesis and vascular leakage that expands the hematoma

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Scalia, *et al*, *Br J Neurosurg* 2022 Jan 8, 1-6

Cyst formation after SRS for brain AVM

- 2,619 patients across 22 studies
- 78 developed post-SRS cyst formation (3.0%)
- 64 had symptomatology and management data
- 21 (32.8%) were symptomatic and treated with surgical intervention
- 43 (67.2%) were managed conservatively
- Mean latency period to post-SRS cyst formation was 6.5 years

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Ilyas, *et al*, *J Neurosurg* 2018; 128: 1354-1363

Cyst formation after SRS for brain AVM

- Uncommon complication with long latency period
- Majority are asymptomatic and can be managed conservatively
- Enlarging or symptomatic cysts may require surgical intervention
- Mean rates of… (based on pooled data)
  - Symptomatic radiation-induced changes: 8.6%
  - Post-SRS hemorrhage: 8.8%
  - Mortality: 6.0%

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Ilyas, *et al*, *J Neurosurg* 2018; 128: 1354-1363

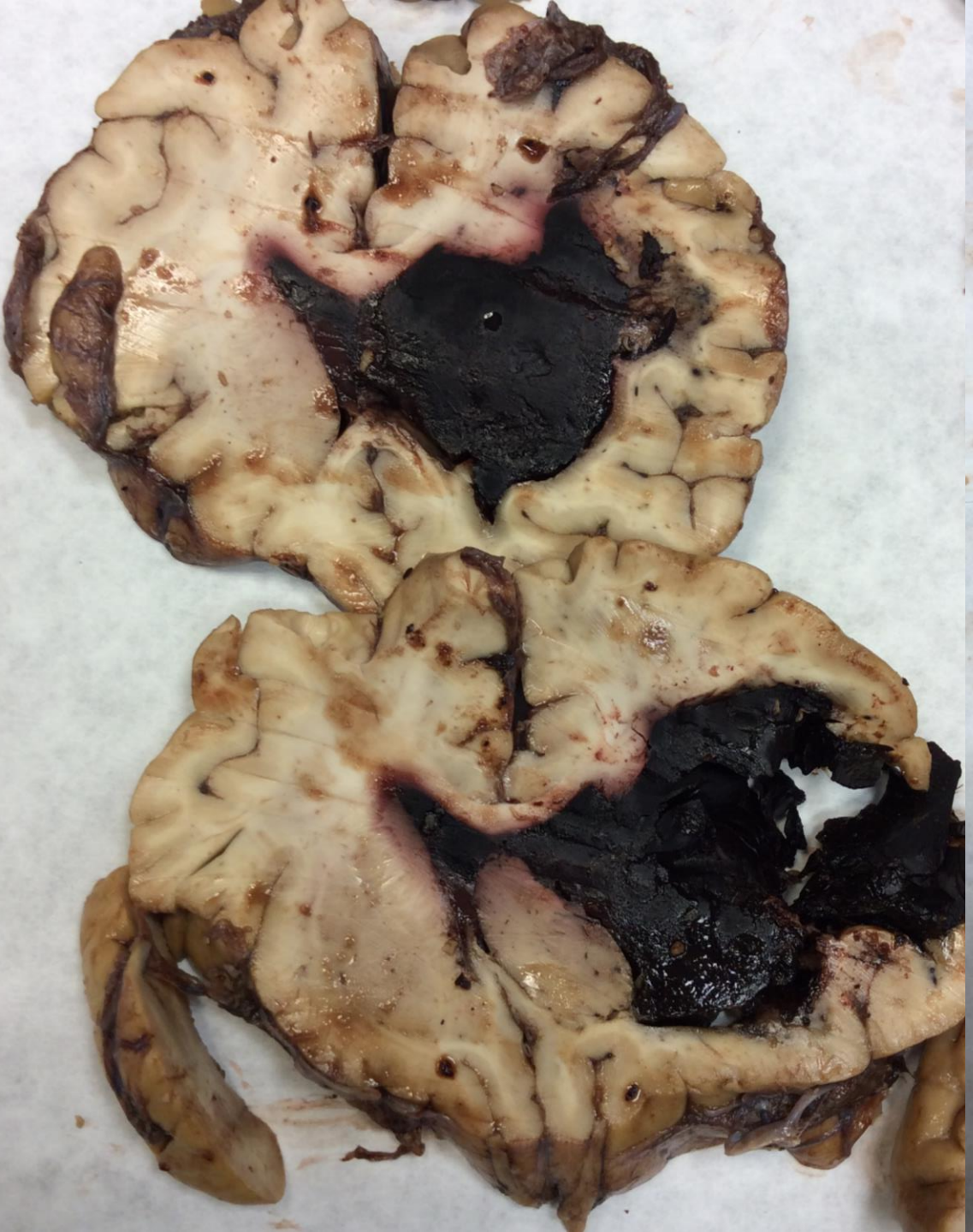
Cause of death

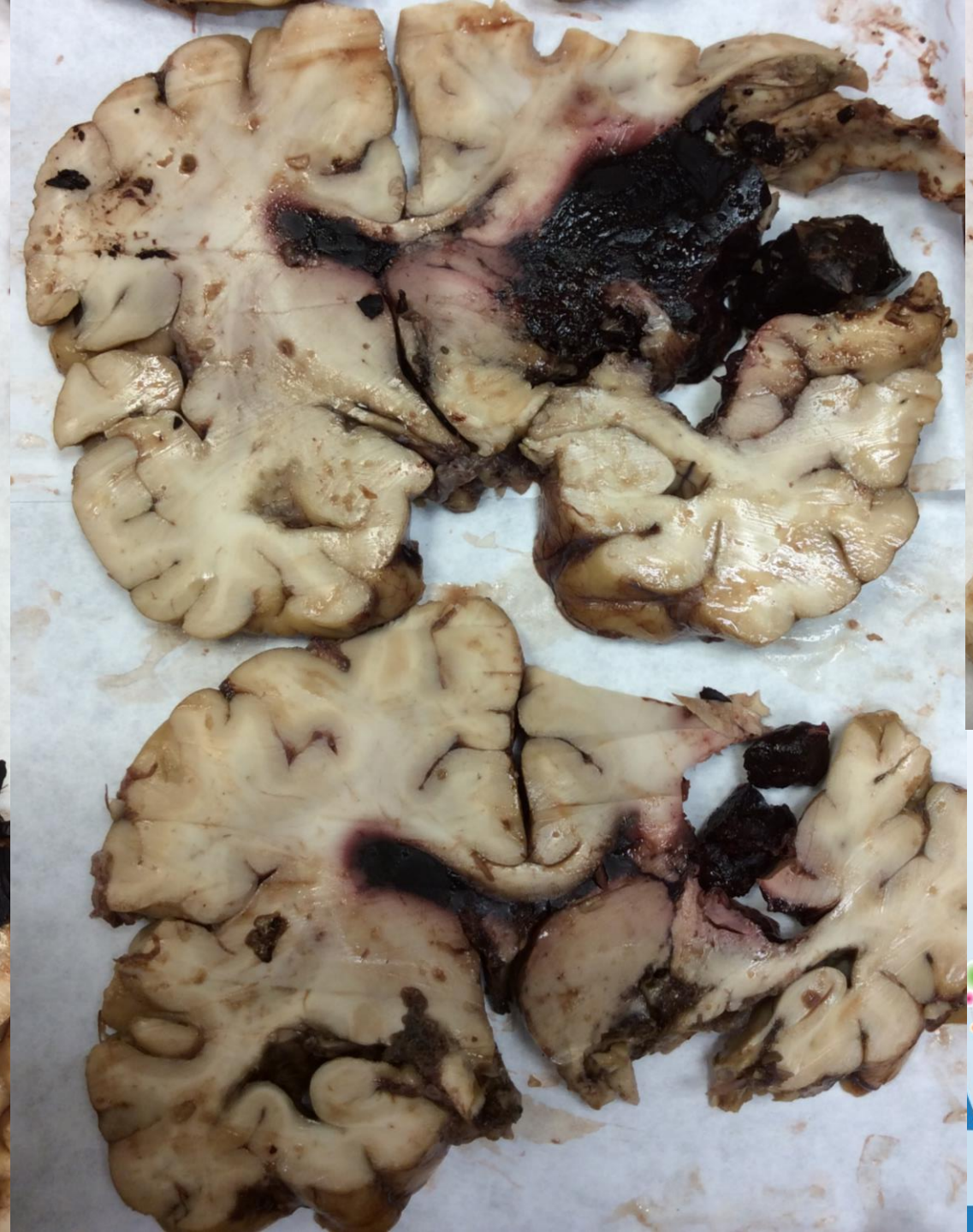
- Likely related to gradually worsening mass effect and rising intracranial pressure
  - Chronic encapsulated intracerebral hematoma
  - Cyst formation
- Cerebellar tonsillar herniation: finally reached the tipping point

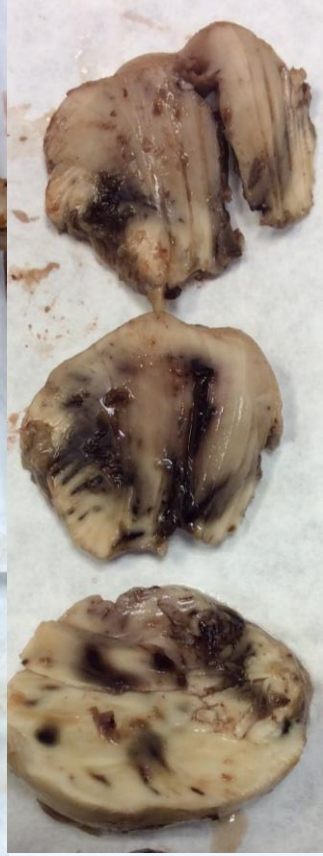
CASE #2

History

- Consult from JFK Medical Center in Edison, NJ
- 63-year-old man who underwent a right carotid endarterectomy for stenosis and did well immediately post-op
- On post-op day #3, became unresponsive.
- Head CT showed massive right-sided intracerebral hemorrhage
- Made comfort measures-only







Final Neuropathologic Diagnosis

- Intracerebral hemorrhage, very large, right cerebral hemisphere, with extension into the ventricular system, cerebral edema, right-to-left midline shift, subfalcine and transtentorial herniation, and Duret hemorrhages
- Clinical history of recent right carotid endarterectomy

Intracerebral hemorrhage after carotid endarterectomy

- Pomposelli FB, Lamparello PJ, Riles TS, Craighead CC, Giangola G, Imparato AM, “Intracranial hemorrhage after carotid endarterectomy,” *J Vasc Surg* 1988; 7: 248-255 (February)
- Piepgras DG, Morgan MK, Sundt TM Jr, Yanagihara T, Mussman LM, “Intracerebral hemorrhage after carotid endarterectomy,” *J Neurosurg* 1988; 68: 532-536 (April)

Intracerebral hemorrhage after carotid endarterectomy

- 1,500 CEAs (1975-1984)—New York University
- 11 (0.7%) complicated by postop ICH
- Mortality 36%
- ICH occurred anywhere from immediately postop to 10 days later (mean 3.3 days)

Pompselli FB, *et al*, *J Vasc Surg* 1988; 7: 248-255

Intracerebral hemorrhage after carotid endarterectomy

- 2,362 consecutive CEAs (1972-1986)—Mayo Clinic
- 14 (0.6%) postop ICHs
- All within first two weeks postop
- All ipsilateral to the side of surgery
- 8 deaths (57% mortality)

Piepgras DG, *et al*, *J Neurosurg* 1988; 68: 532-536

Intracerebral hemorrhage after carotid endarterectomy

- 2,747 consecutive CEAs (1990-1999)—Mayo Clinic
- 12 (0.4%) postop ICHs
- All within first 8 days postop
- All ipsilateral to the side of surgery
- 7 deaths (58% mortality)
- Of 8 patients with cerebral blood flow measurements, 5 had greater than 100% increase (“doubling”)

Henderson RD, *et al*, *J Neurosurg* 2001; 95: 964-9

Intracerebral hemorrhage after carotid endarterectomy: risk factors/mechanisms

- Pre- and postoperative hypertension
- Chronic hemispheric hypoperfusion with impaired autoregulation
- Relief of high-grade carotid stenosis with subsequent hyperperfusion
- Perioperative cerebral ischemia
- Anticoagulation

Piepgras DG, *et al*, *J Neurosurg* 1988; 68: 532-536
Henderson RD, *et al*, *J Neurosurg* 2001; 95: 964-9

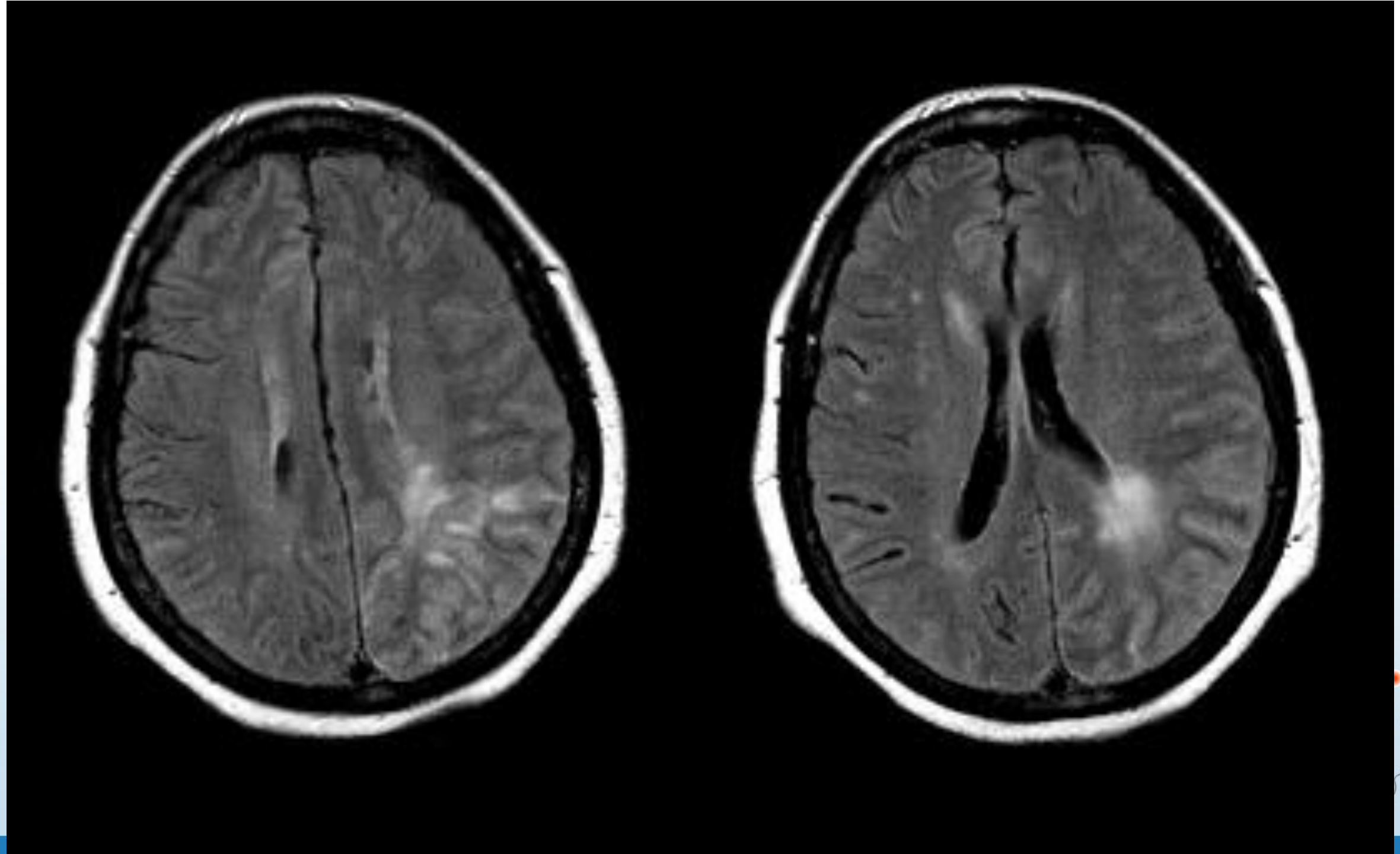
CASE #3

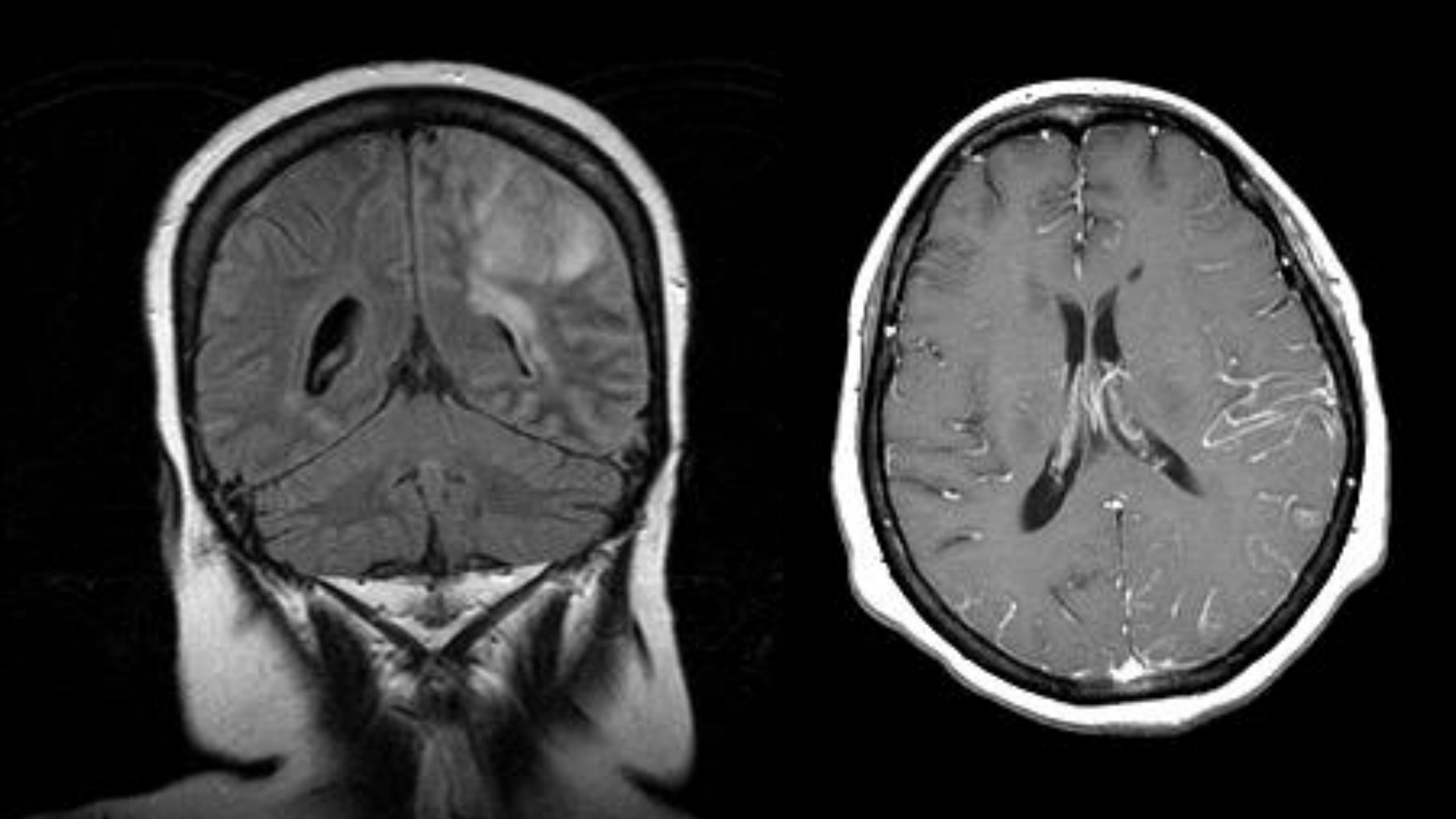
History

- 71-year-old woman with headaches and fatigue a month prior to admission
- ESR elevated; temporal artery biopsy negative
- Continued to have throbbing headaches, confusion, disorientation, and fever as high as 102^{o}
- Presented to doctor's office and sent to E.R.

History

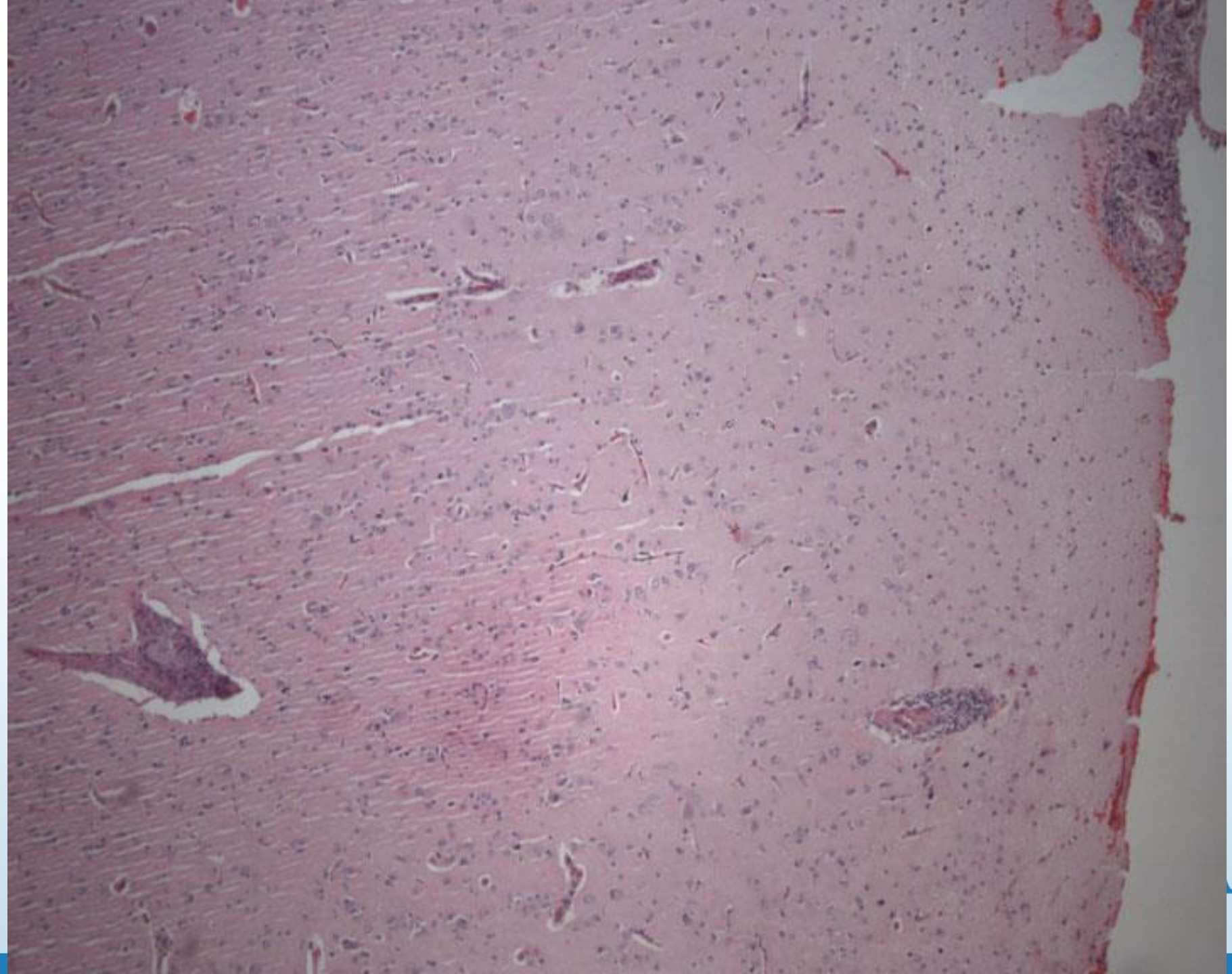
- Past medical history
  - Hypertension (on atenolol)
  - Hyperlipidemia (on atorvastatin)
  - Diabetes mellitus (on glipizide extended release)
  - S/P cholecystectomy, appendectomy, right total knee replacement, partial right mastectomy for presumably benign breast mass
  - No known drug allergies
- Non-focal neurologic examination

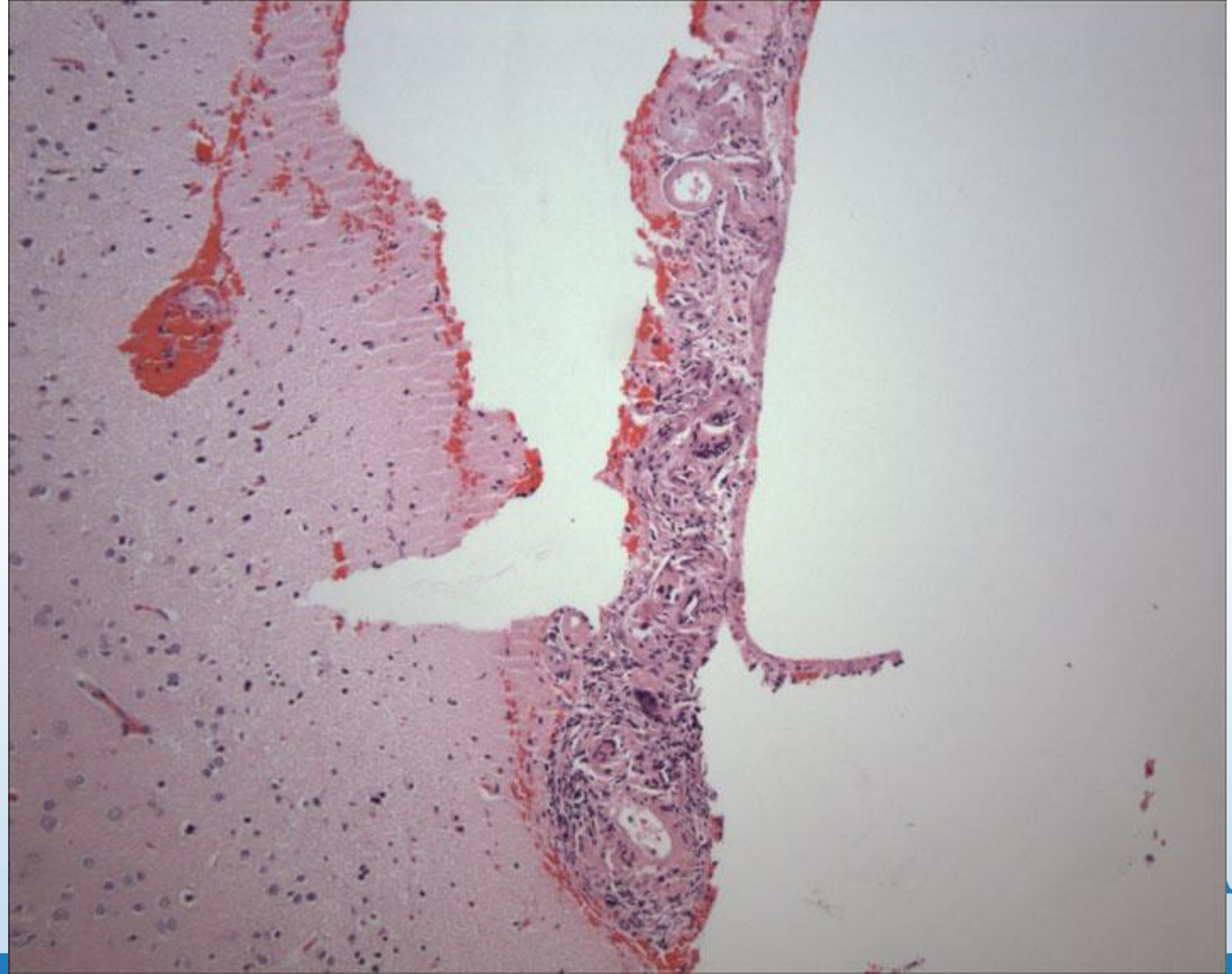


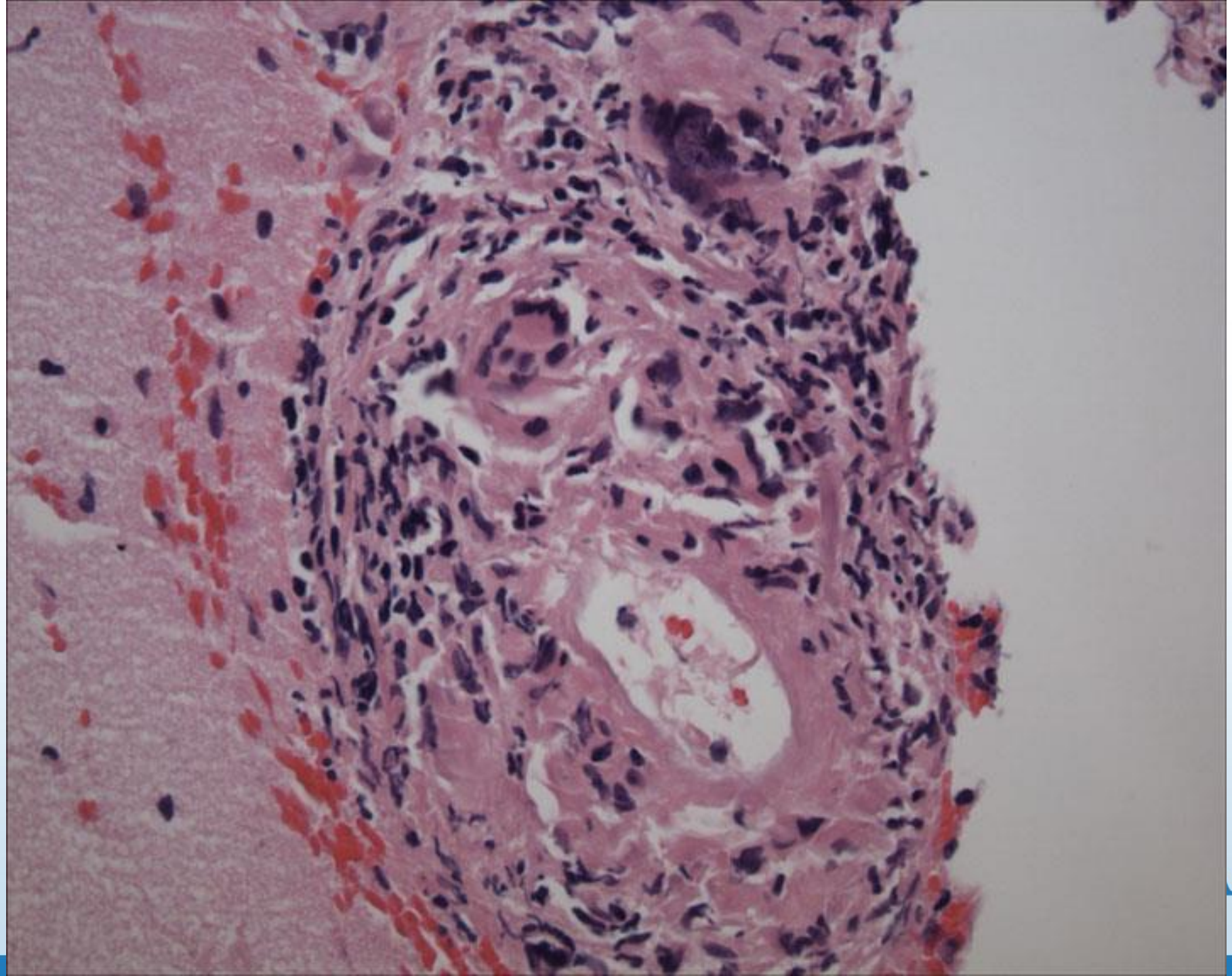


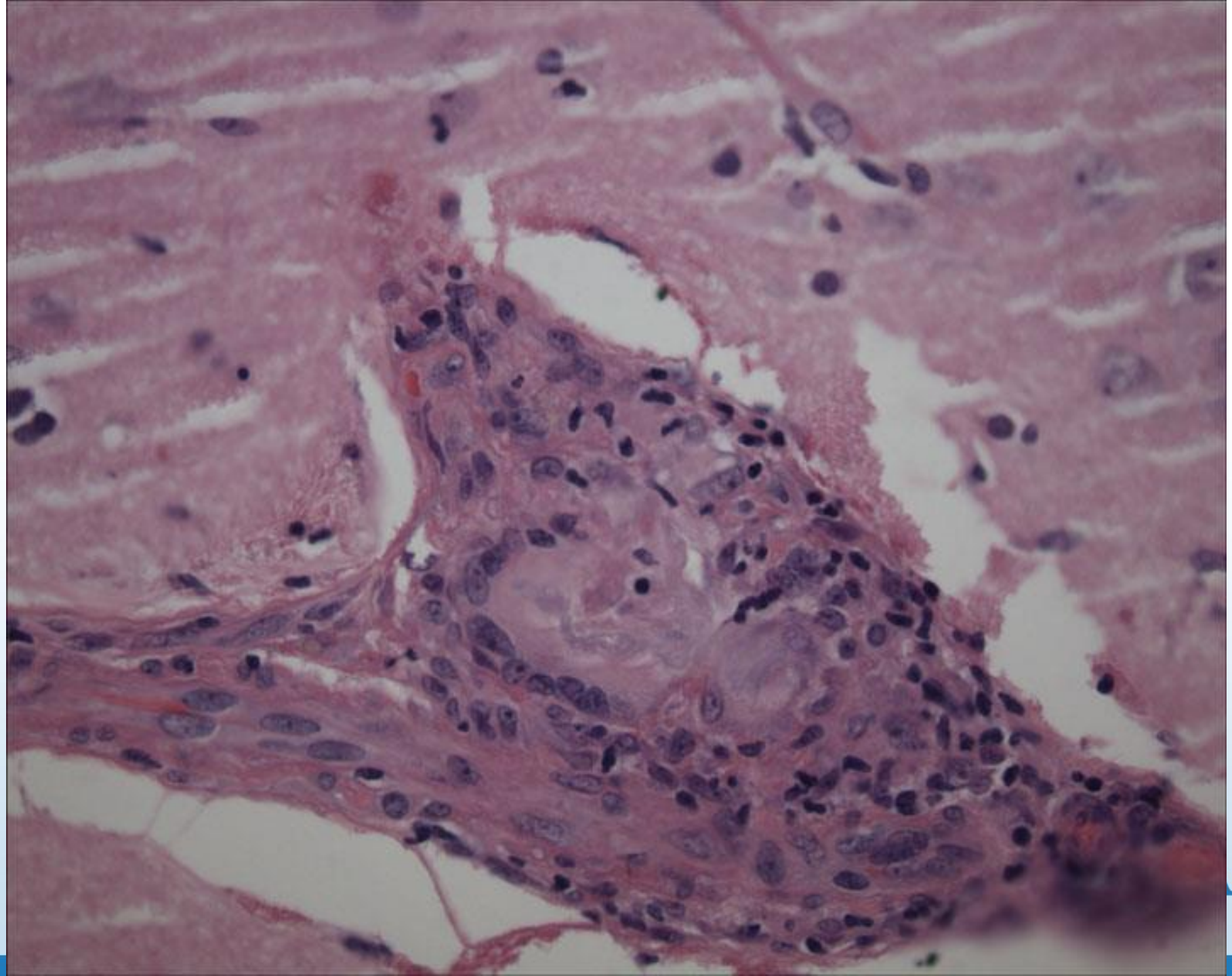
History

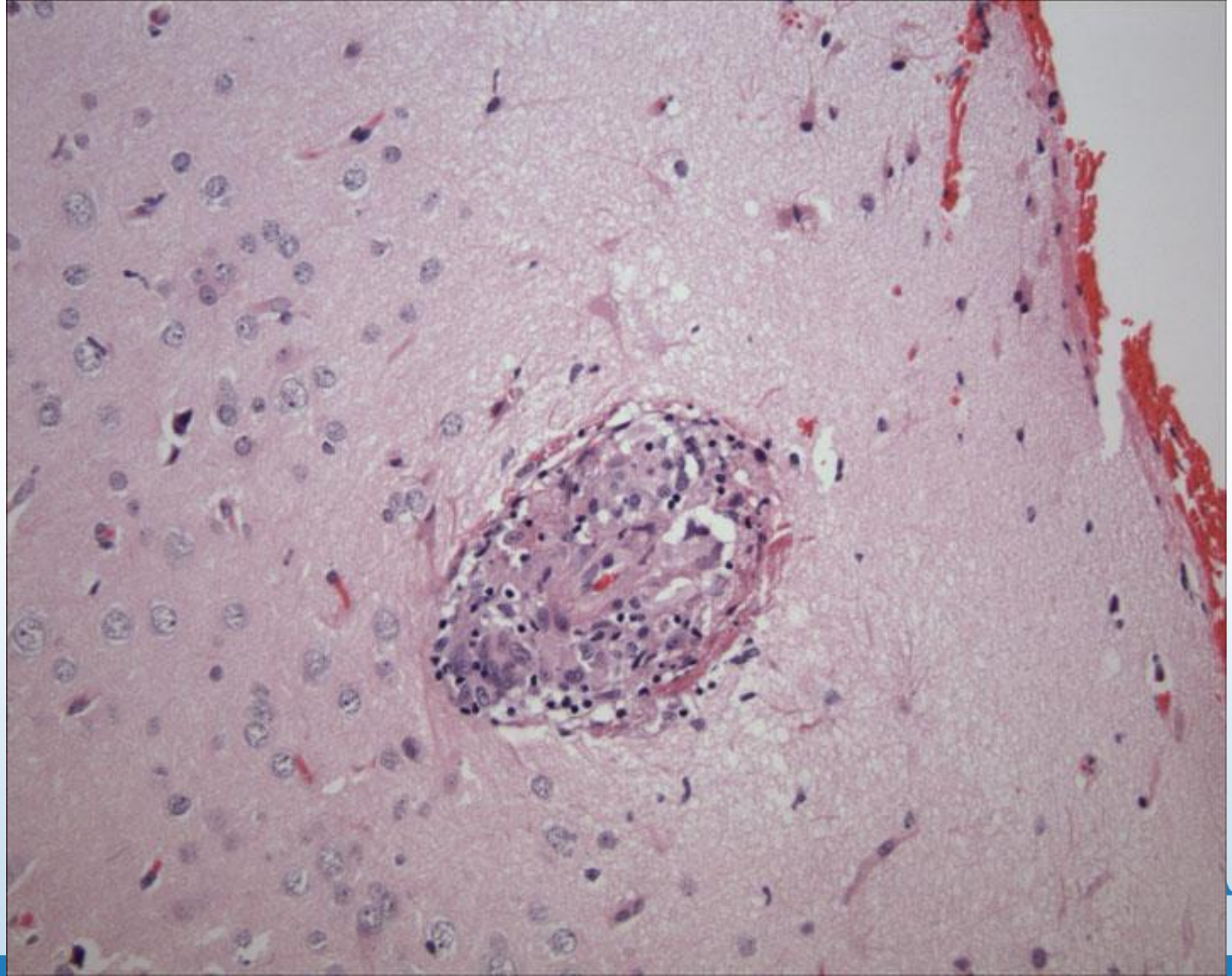
- Lumbar puncture: 20 WBC, protein 235
- Started on acyclovir for possible encephalitis
- MRA completely normal
- Had a brain biopsy in 2006

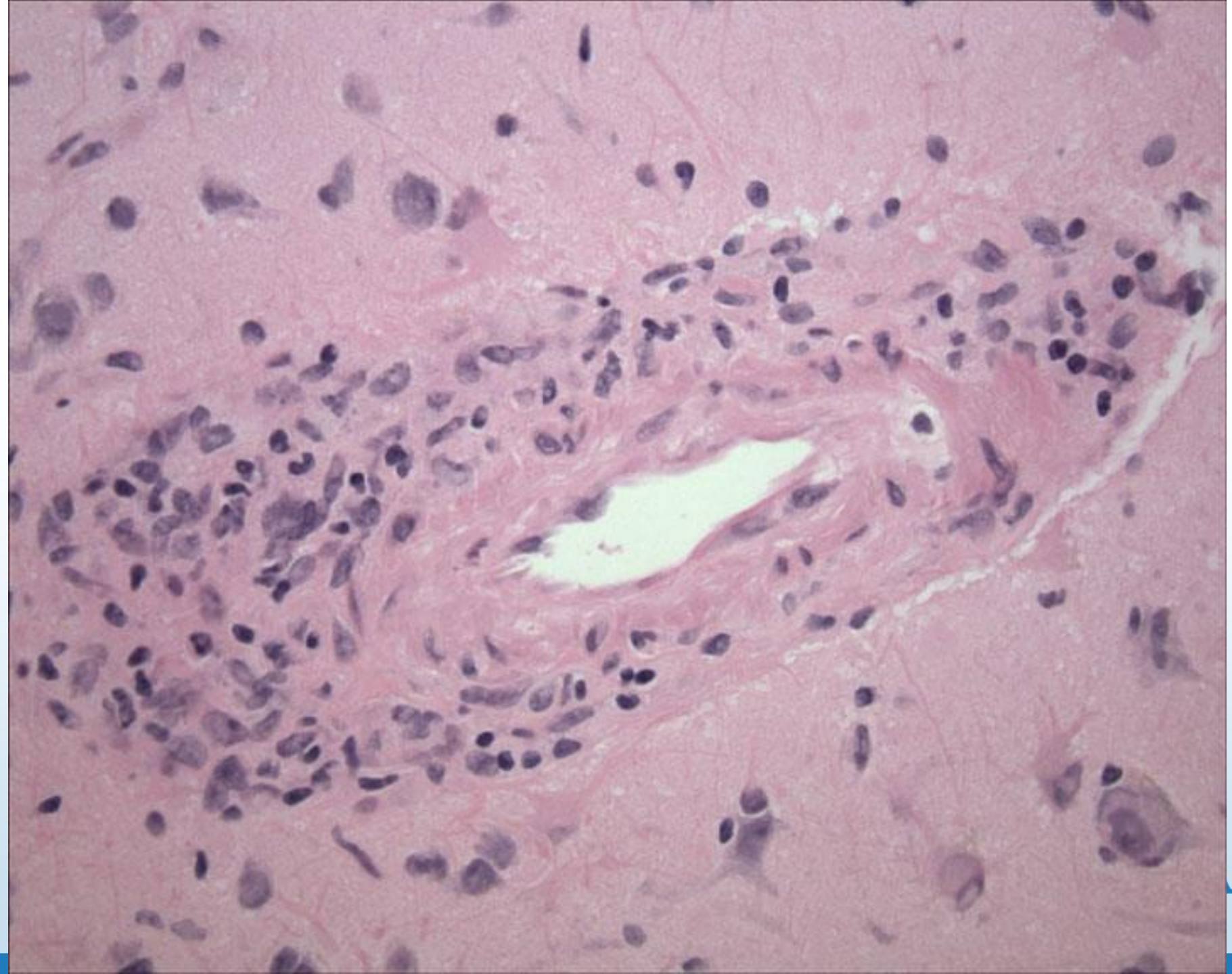


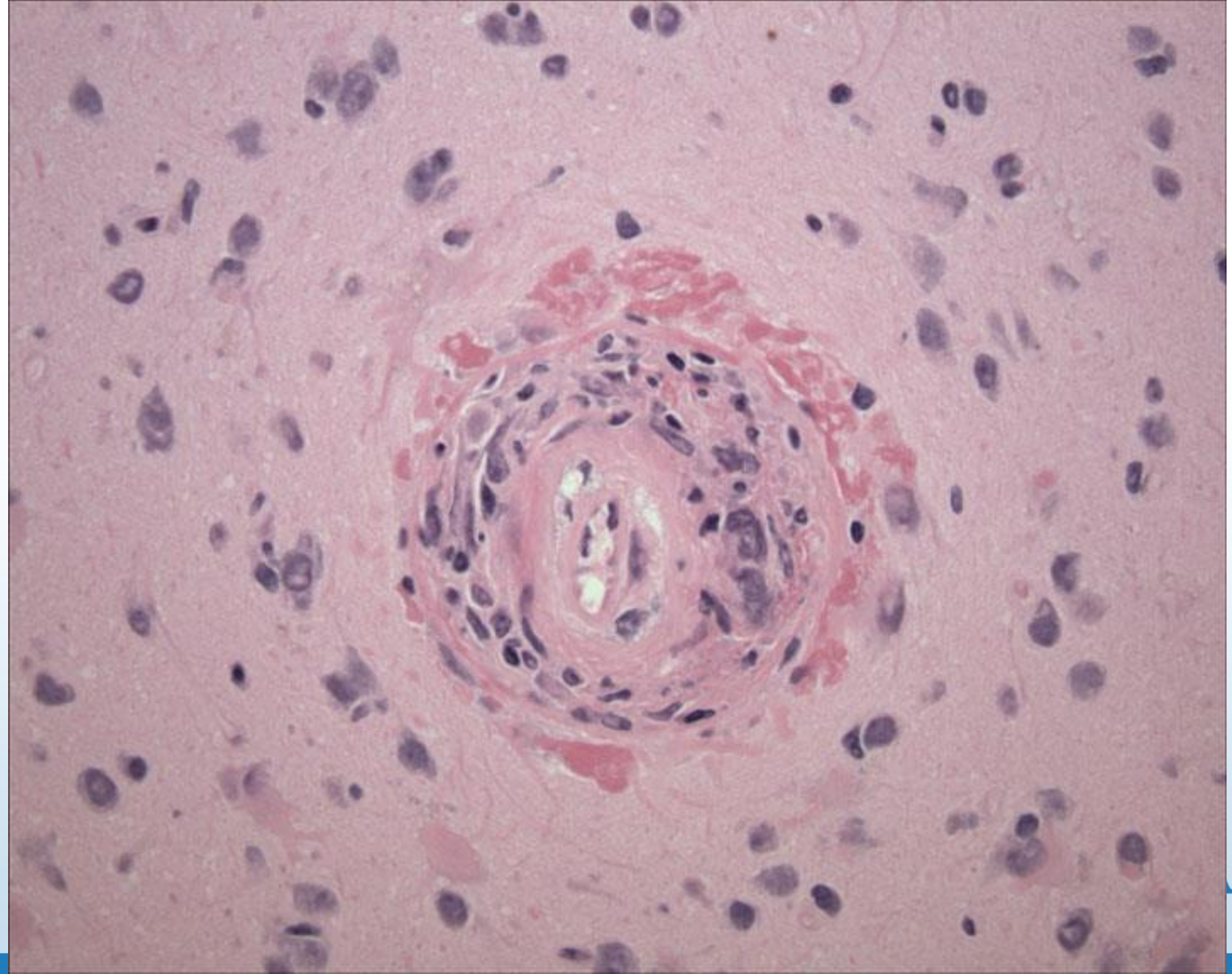


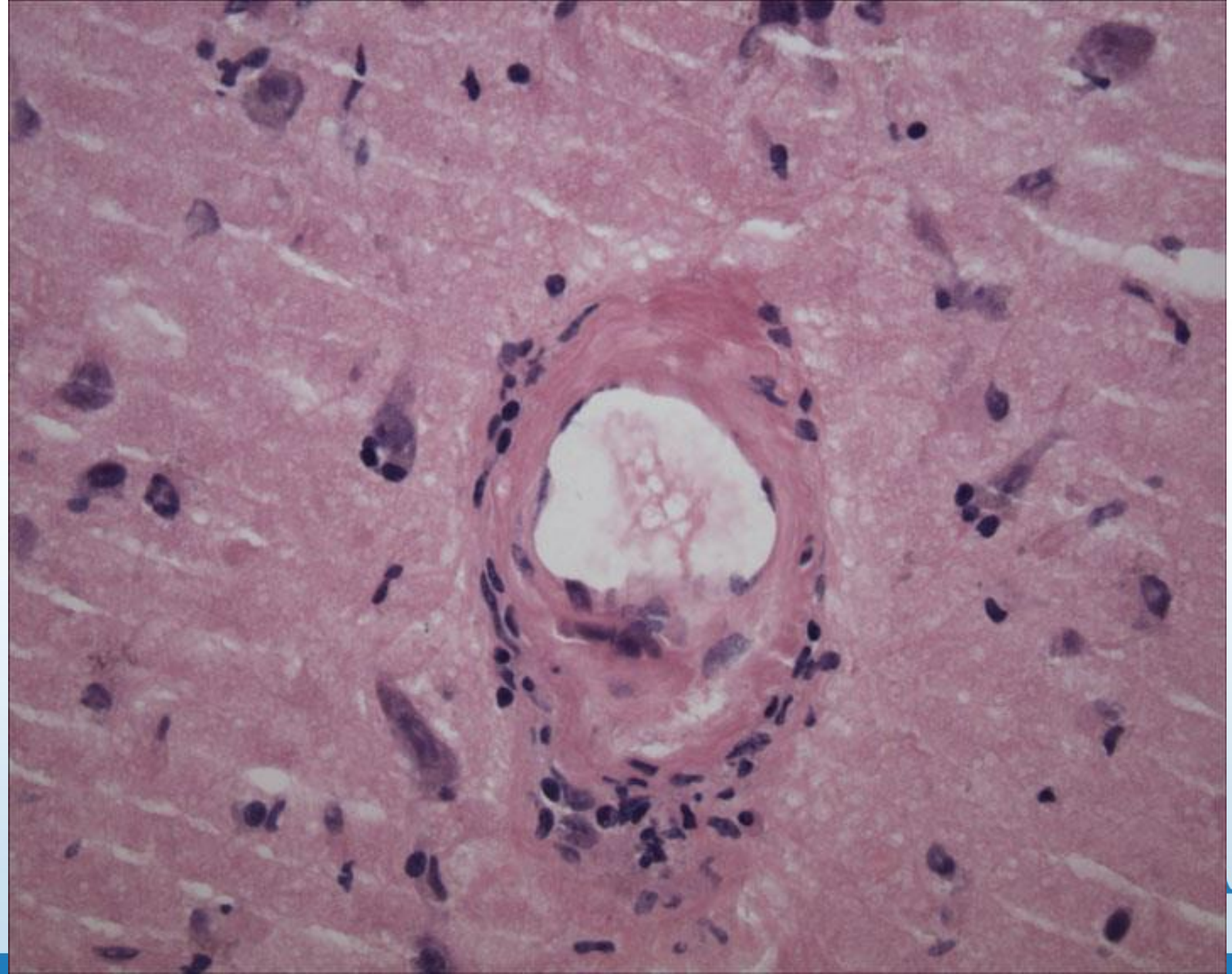


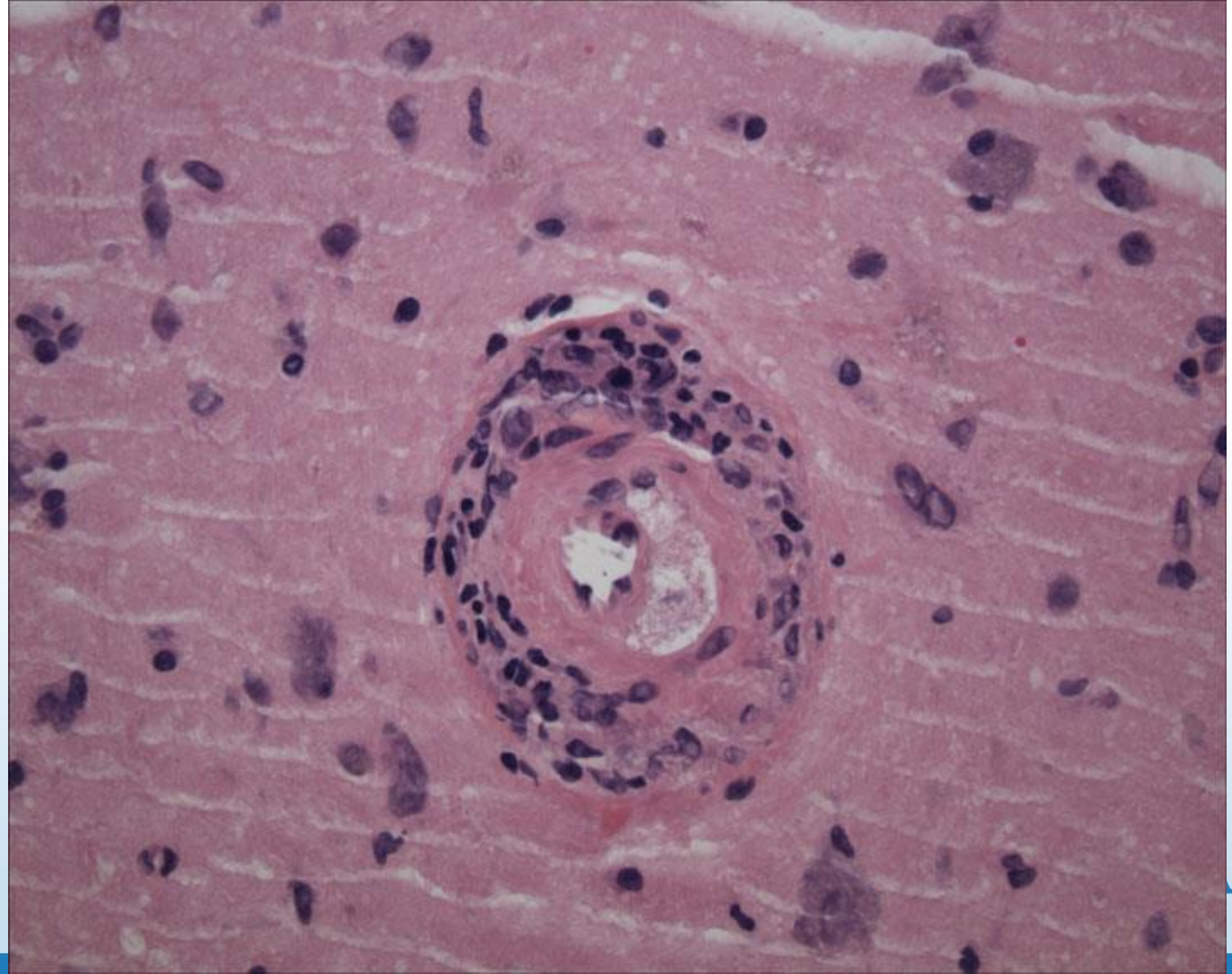


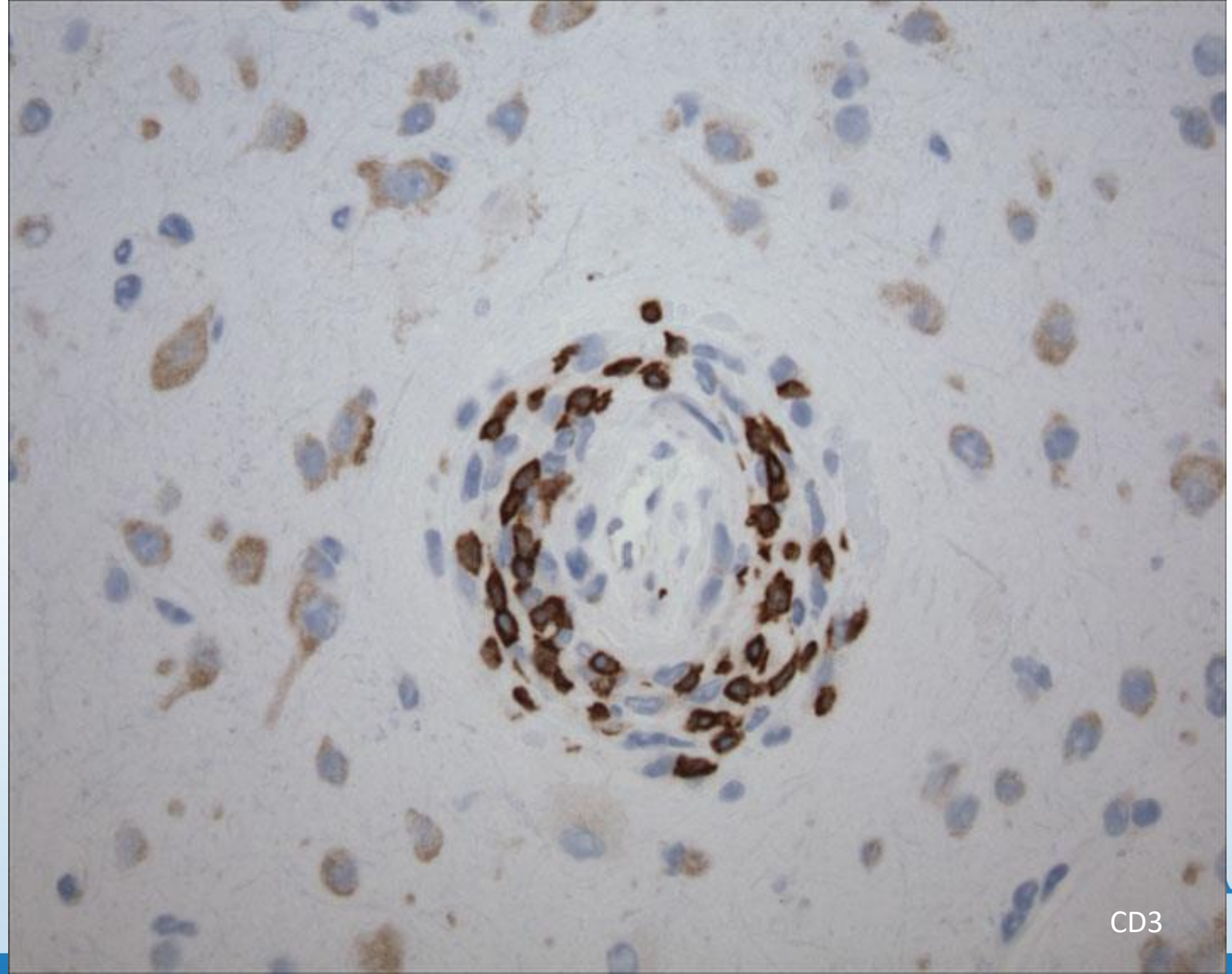












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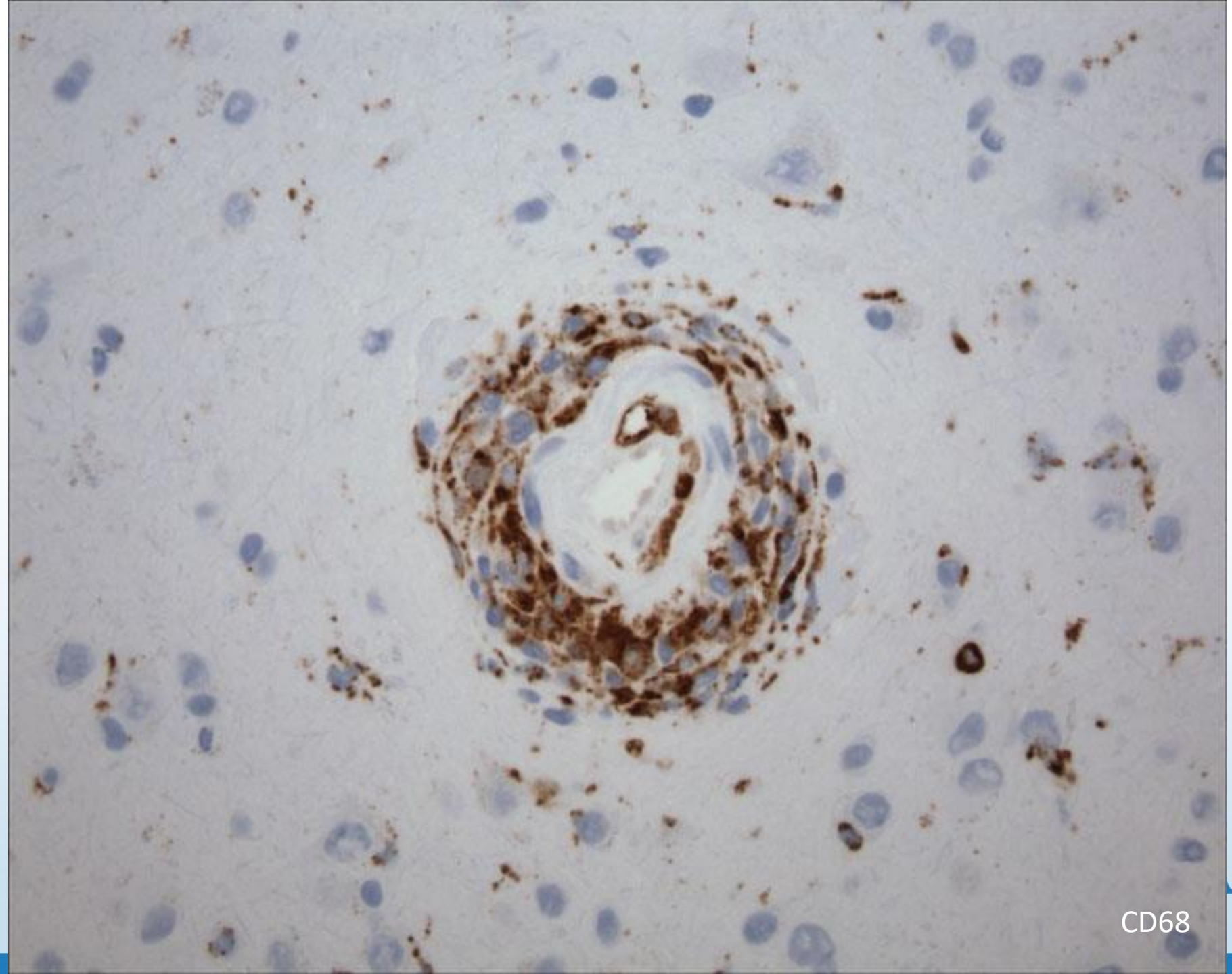

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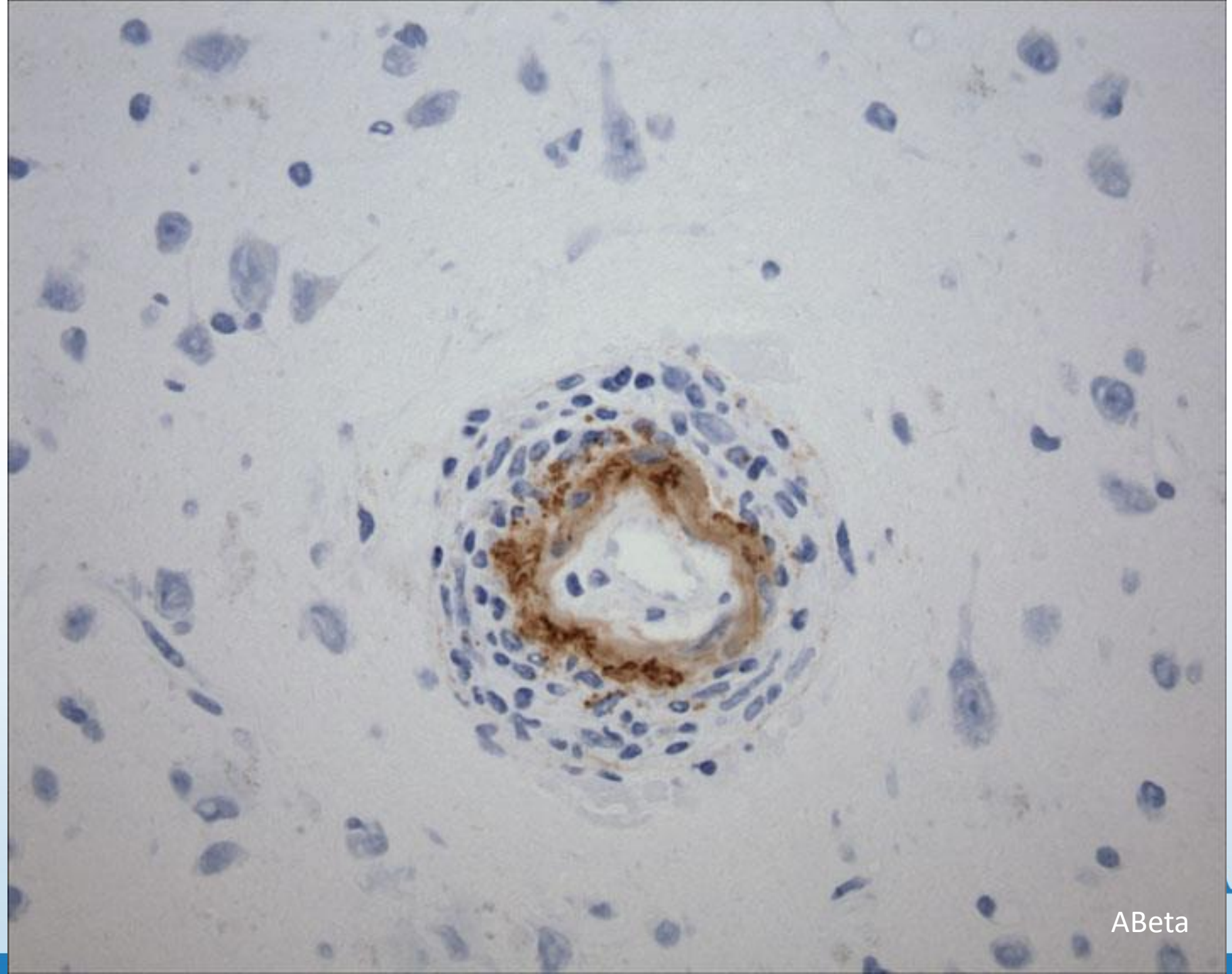

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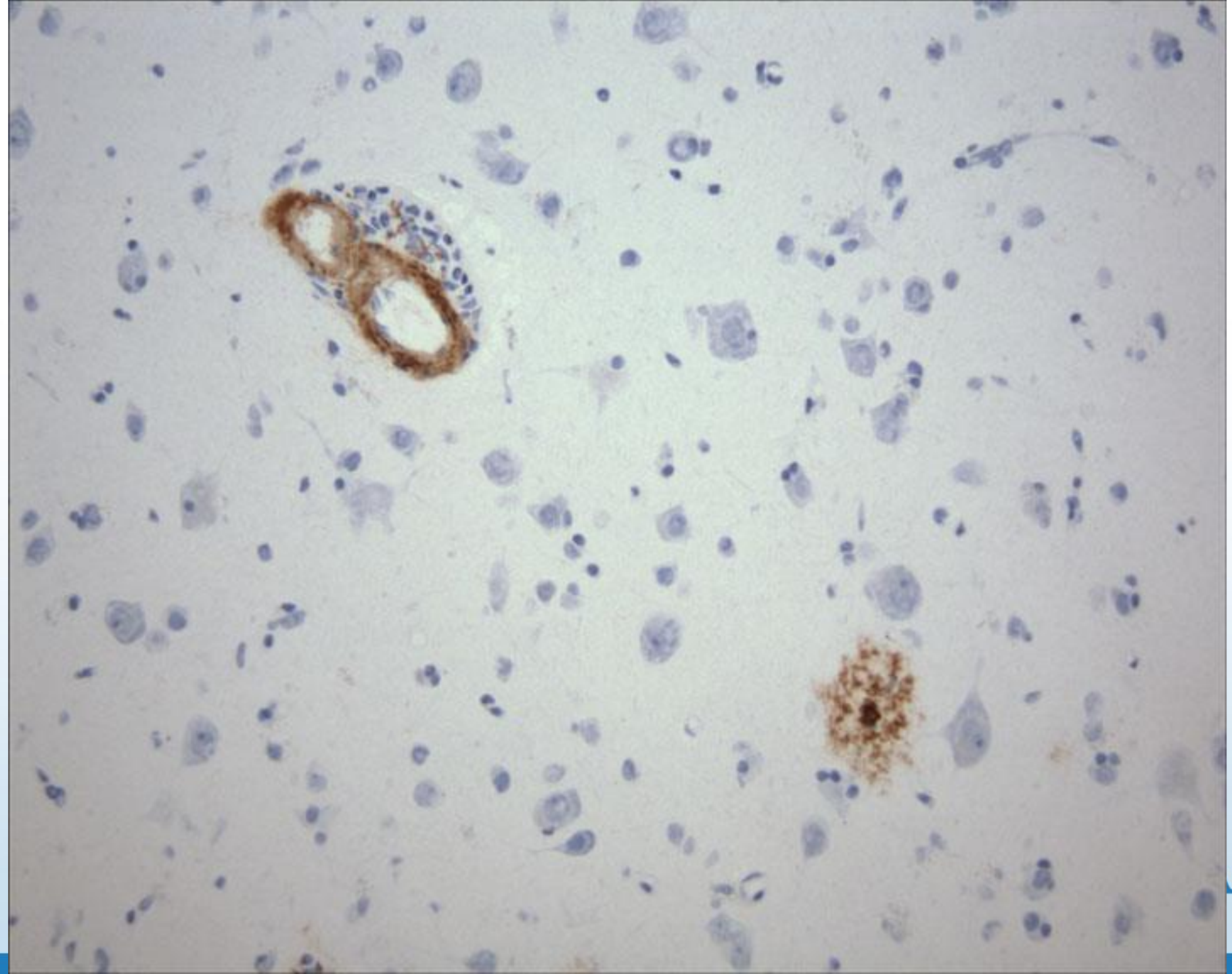
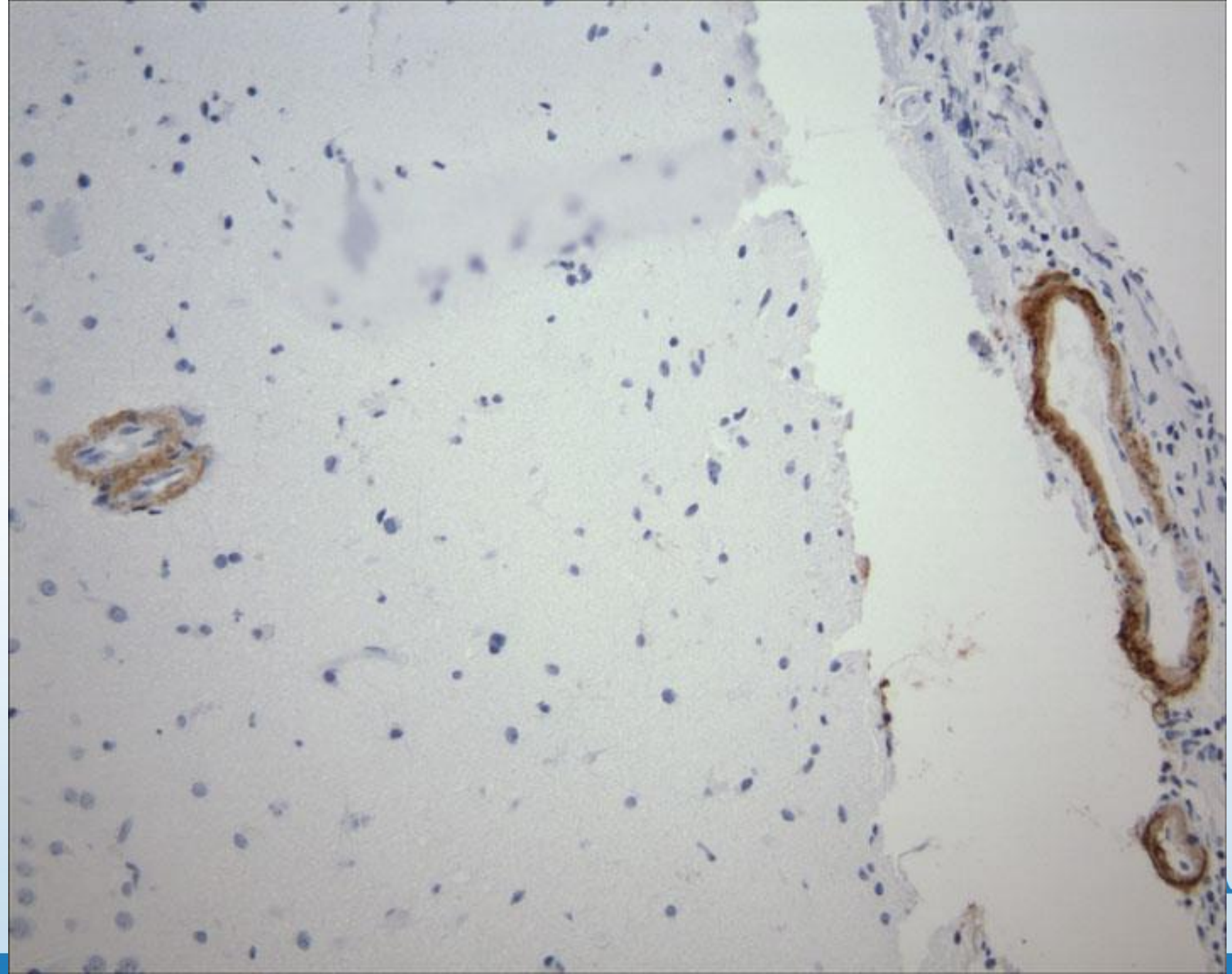
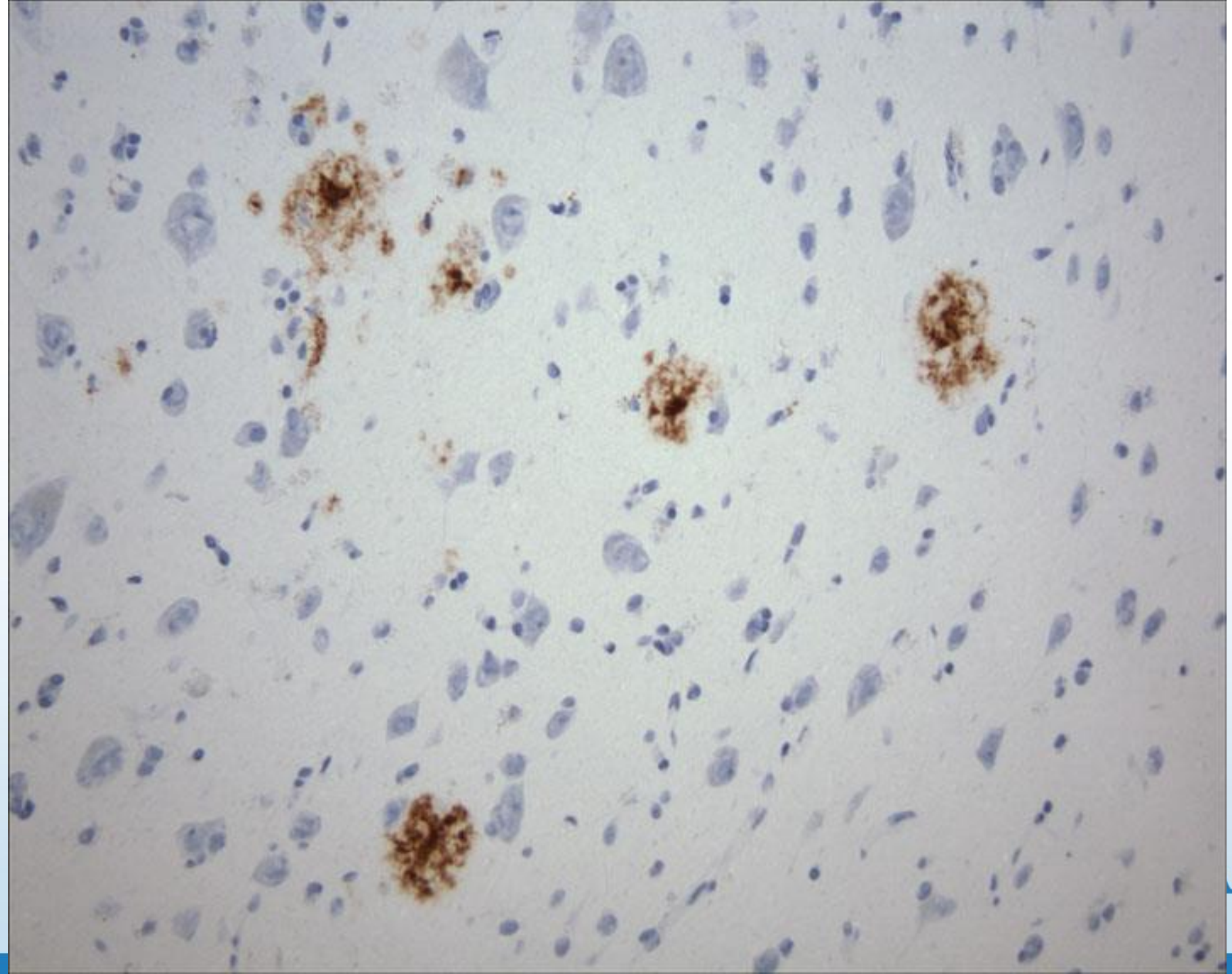






FINAL NEUROPATHOLOGIC DIAGNOSIS

GRANULOMATOUS ANGIITIS WITH CEREBRAL AMYLOID ANGIOPATHY (Aβ-RELATED ANGIITIS)

AANP

Cerebral amyloid angiopathy (CAA)

- Deposition of amyloid-β (Aβ) in the adventitia and media of cortical and meningeal blood vessels
- Amyloid is similar that observed in the plaques of Alzheimer disease (AD)
- Can lead to lobar intracerebral hemorrhage
- In a subset of patients, vascular inflammation is also present
  - CAA-related inflammation (CAA-RI)—perivascular and non-destructive
  - Aβ-related angiitis (ABRA)—vasculitis, transmural, often granulomatous
- Can lead to cognitive impairment without AD changes or microhemorrhages (but most often associated with them)

Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603
Lowe J, Kalaria R, "Greenfield's Neuropathology, Ninth Edition," pp. 930-48

Study of Aβ vascular deposition and inflammation

- 62 available pathologic surgical specimens from 1987-2011 (37 open biopsy, 4 stereotactic biopsy, 21 hematoma evacuation)
- 28 cases of ABRA, 40 of CAA, and 10 of CAA-RI
- Compared to 131 consecutive cases of primary CNS vasculitis (PCNSV)—41 diagnosed by biopsy and the rest by classic angiograms; 13 were ultimately diagnosed with ABRA and placed in that group, leaving 118 cases of non-amyloid PCNSV

Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603

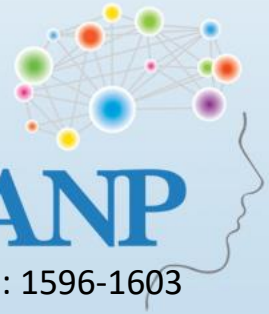
Comparison of ABRA, CAA-RI, CAA, and PCNSV

- ABRA: 28 cases (13 male), avg. age 66, 1.6 months to dx
- CAA-RI: 10 cases (6 male), avg. age 72, 1.2 months to dx
- CAA: 40 cases (18 male), avg. age 71, 0.7 months to dx
- PCNSV: 118 cases (50 male), avg. age 47, 1.4 months to dx
- Statistical analyses not performed on CAA-RI because of too few cases
- ABRA and CAA-RI may be part of the same pathologic spectrum, but the evidence is not definitive

Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603

Comparison of ABRA, CAA-RI, CAA, and PCNSV

- Characteristics of ABRA patients compared to CAA
  - Younger
  - Lower frequency of altered cognition
  - Less frequent neurologic deficit or stroke
  - Lower rate of intracerebral hemorrhage
  - More frequent gadolinium leptomeningeal enhancement on MRI
  - More favorable response to treatment (glucocorticoids, alone or in combination with cyclophosphamide) and better outcome



Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603

Comparison of ABRA, CAA-RI, CAA, and PCNSV

- Characteristics of ABRA patients compared to PCNSV
  - Older
  - Increased frequency of altered cognition and seizures at presentation
  - Reduced frequency of hemiparesis and visual symptoms
  - Significantly higher CSF protein levels
  - Less frequent infarcts
  - More frequent gadolinium leptomeningeal enhancement on MRI
  - Similar response to treatment and outcome

Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603

Conclusions

- ABRA and CAA-RI more closely resemble PCNSV than CAA
- ABRA forms a definable subset of PCNSV
- Vascular inflammation, more than amyloid deposition, has the most impact in causing symptoms

Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C, *Neurology* 2013; 81: 1596-1603

Follow-Up

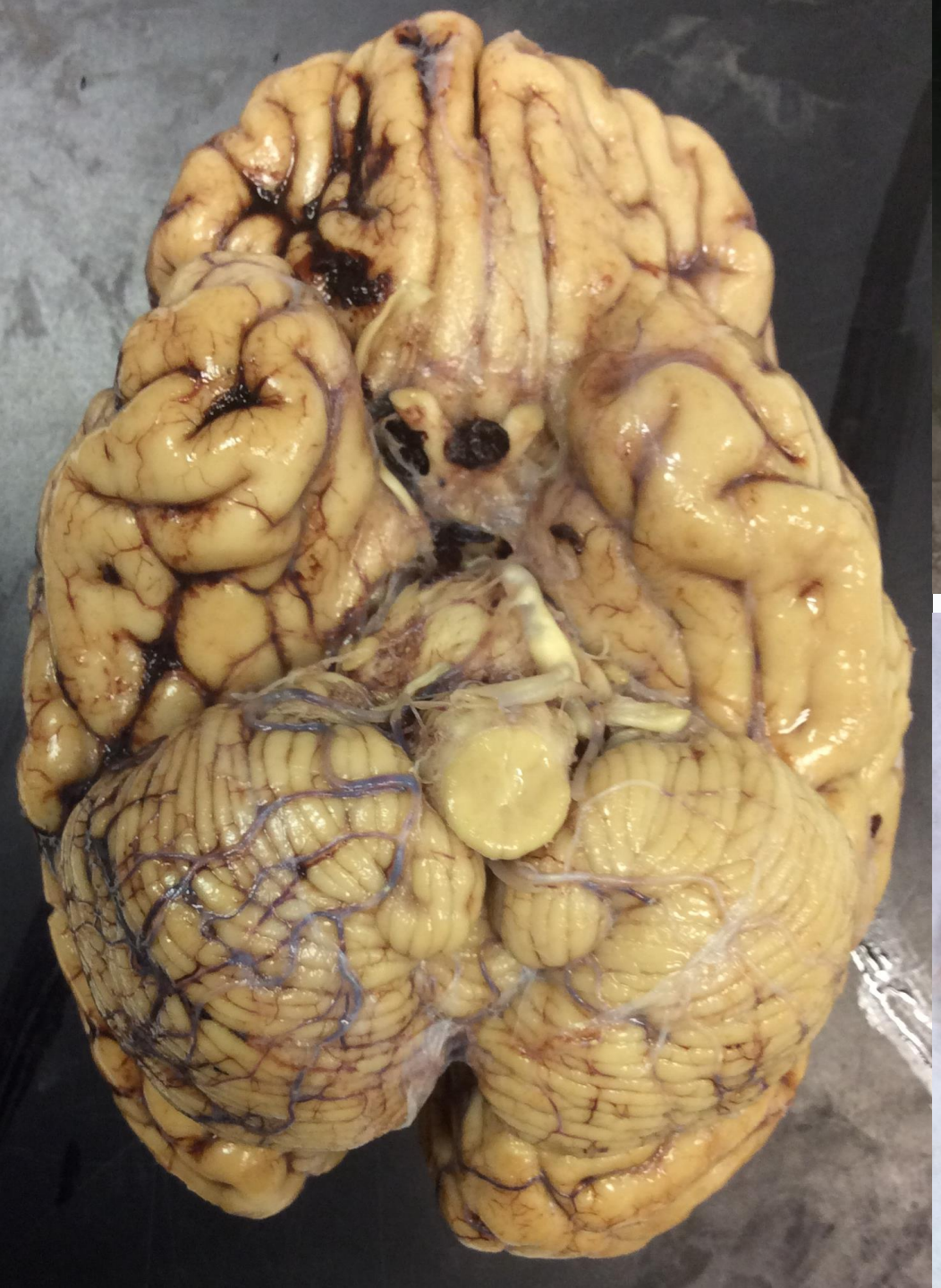
- Treated with high-dose steroids with improvement of symptoms and discharge from hospital on taper
- Now age 87 with multiple active medical problems (HTN, hyperlipidemia, DM, CAD, chronic kidney disease, glaucoma, macular degeneration, fibromyalgia, osteoarthritis, rheumatoid arthritis)
- July 2016—total hip replacement
- Sept. 2017—invasive mucinous adenocarcinoma of sigmoid colon/rectum
- Hospitalized on inpatient psychiatric unit from 5/9 to 6/5/2023 for treatment of agitation, paranoia, and acute hallucinations in the setting of progressive dementia; on donepezil since August 2022; family looking for SNF placement
- This 2006 hospitalization/brain biopsy is never mentioned in the medical record after a discharge summary in February 2007

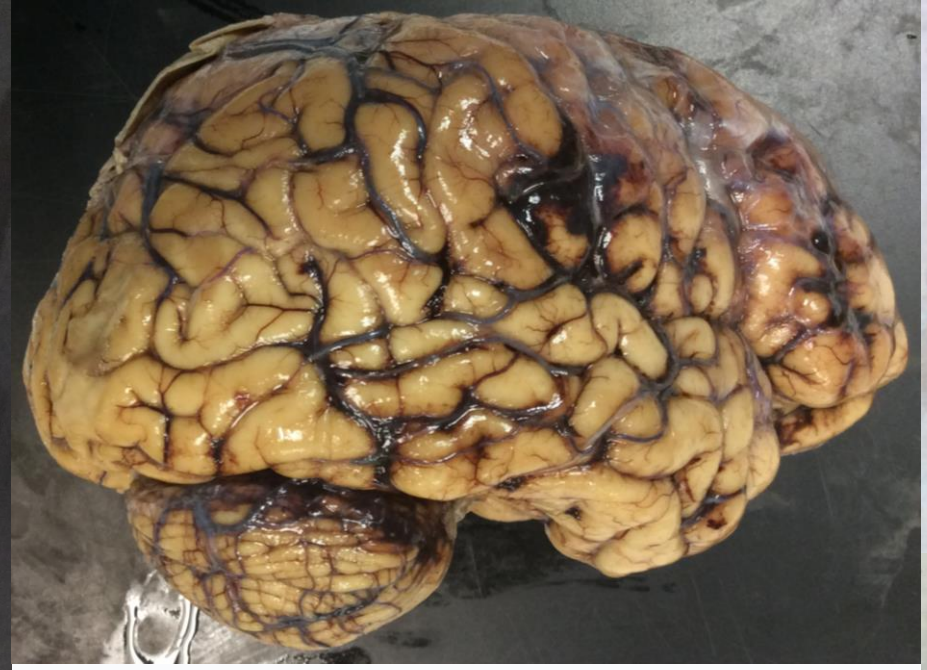
AANP

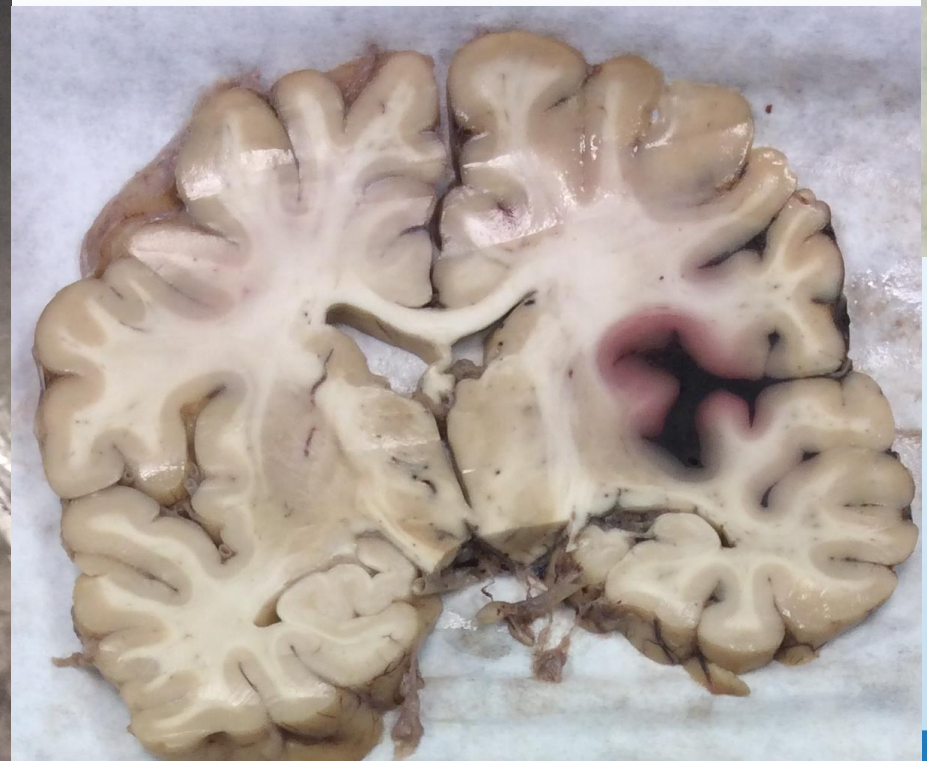
CASE #4

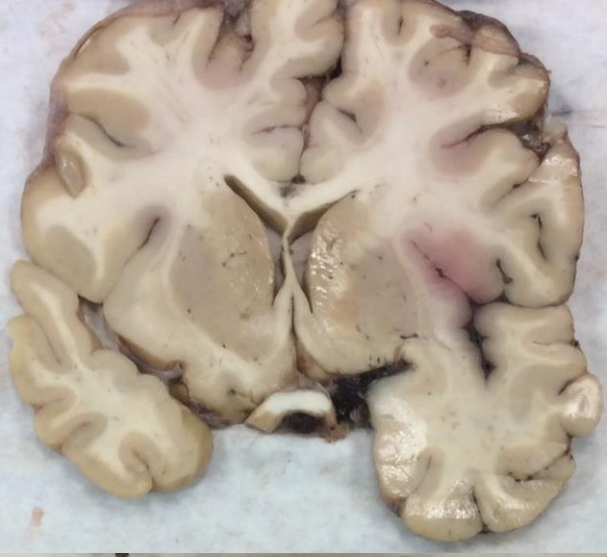
History

- Consult from Bergen County NJ medical examiner office
- 65-year-old woman found down in nursing home bed with large hematoma on forehead
- CT showed “multiple bleeds” in brain
- Bruising all throughout body
- H/O HTN, CVA, COPD, DM, CAD, **dementia**, cervical/uterine cancer, hypothyroidism, bipolar disorder, UTI, cardiac stents, cardiac cath, and old left temporal skull fracture (2016)
- Made CMO and died two days after presentation

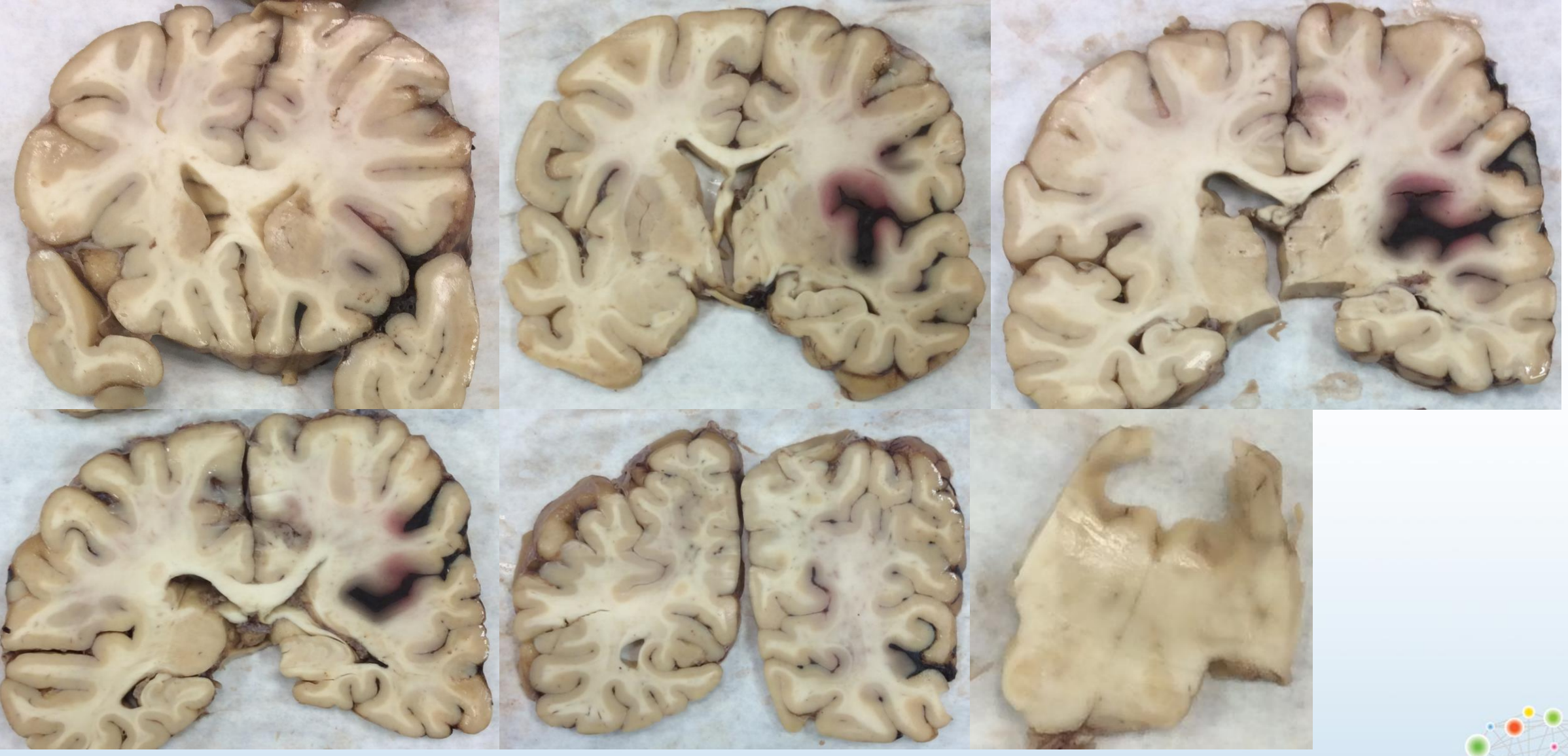




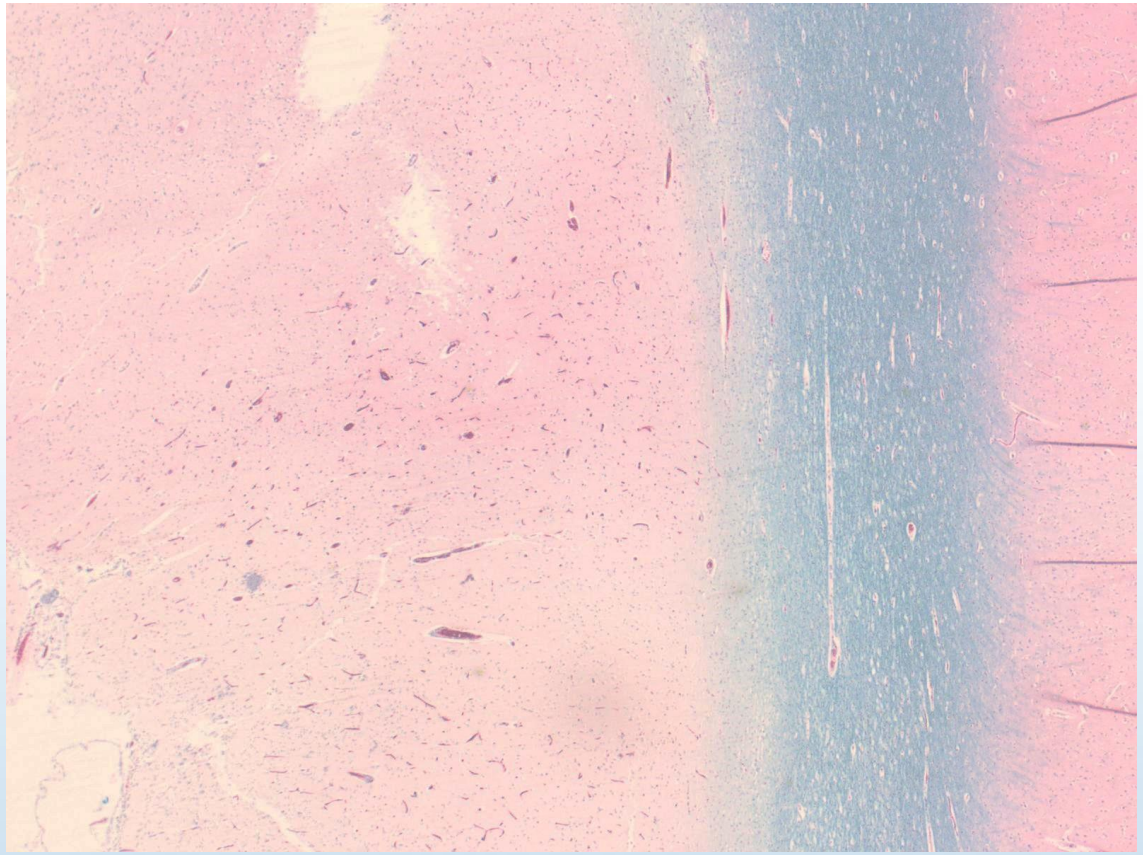


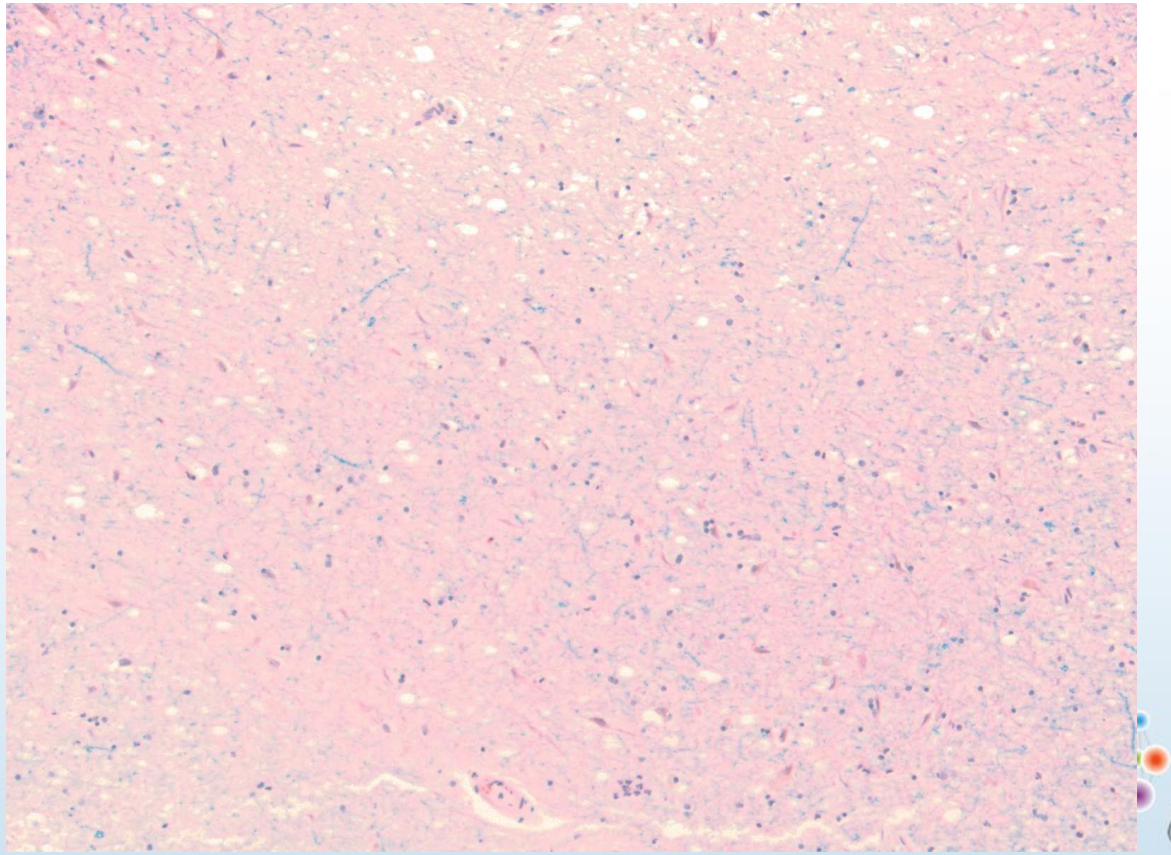


AANP

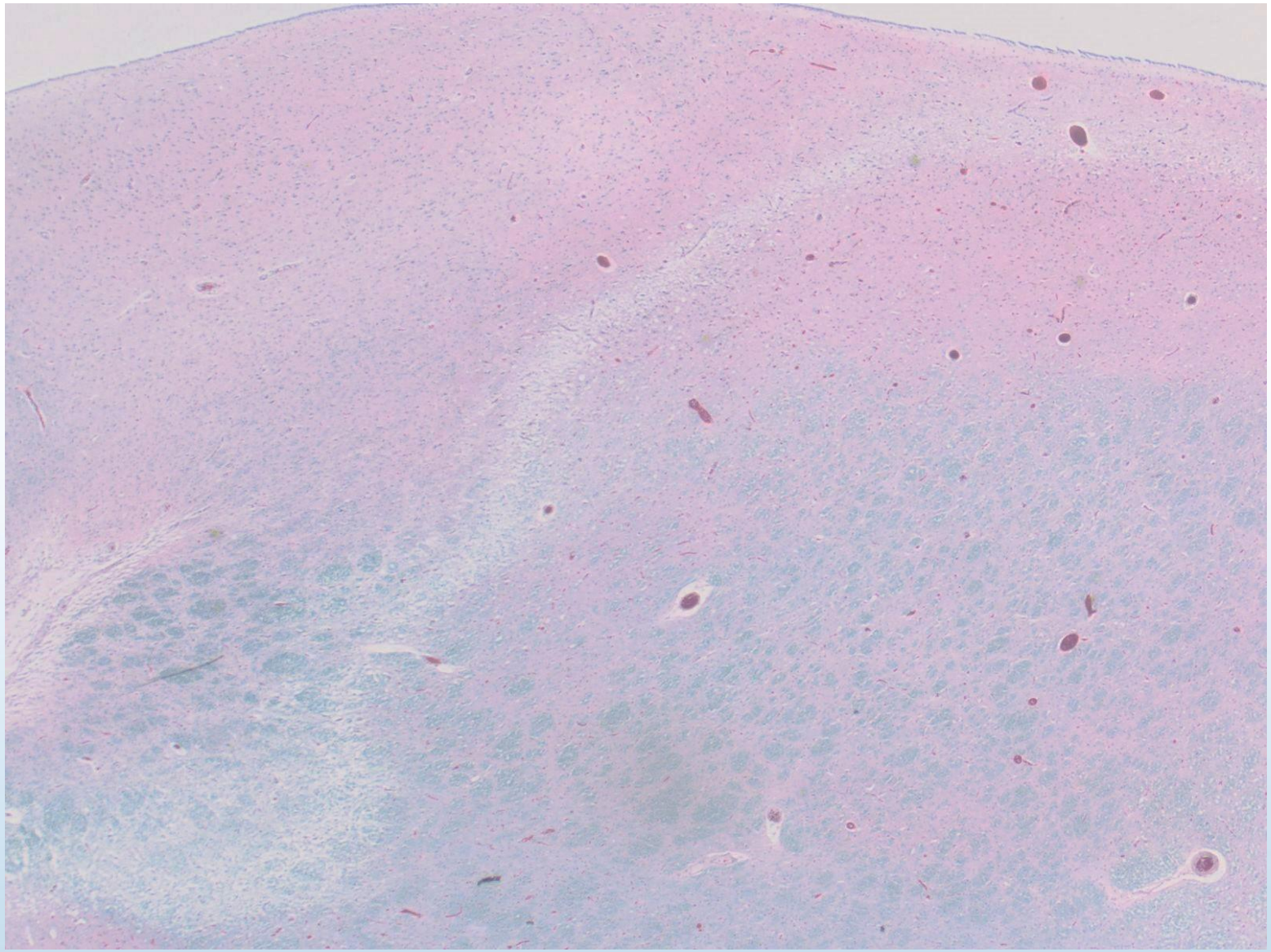


Acute infarcts: right orbitofrontal cortex and substantia innominata

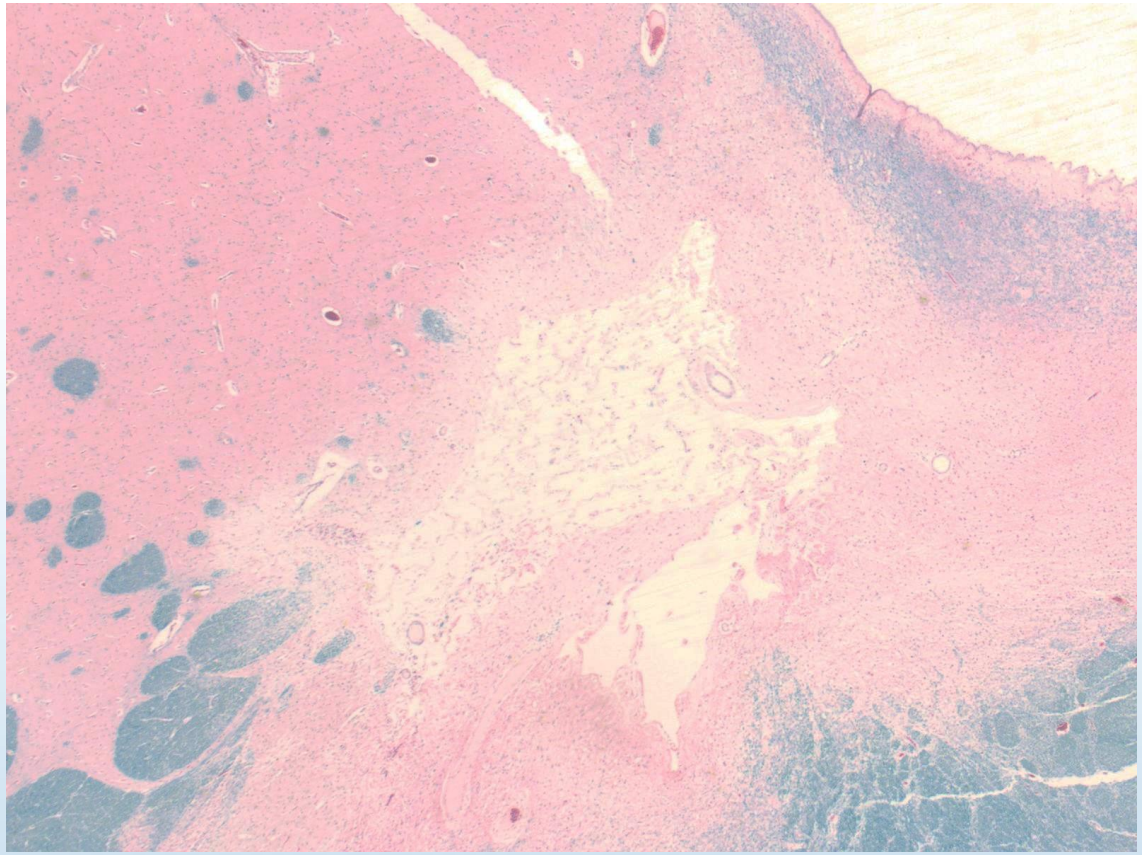


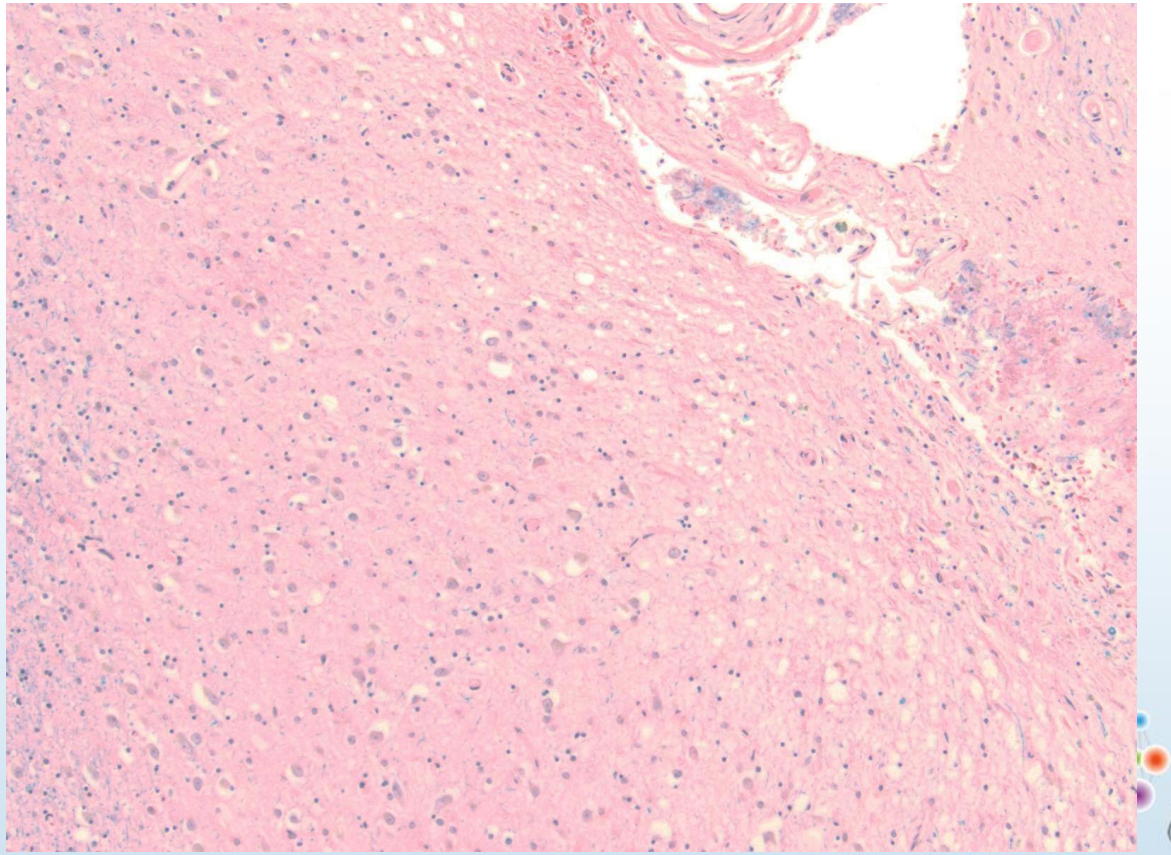


Acute infarct: left thalamus

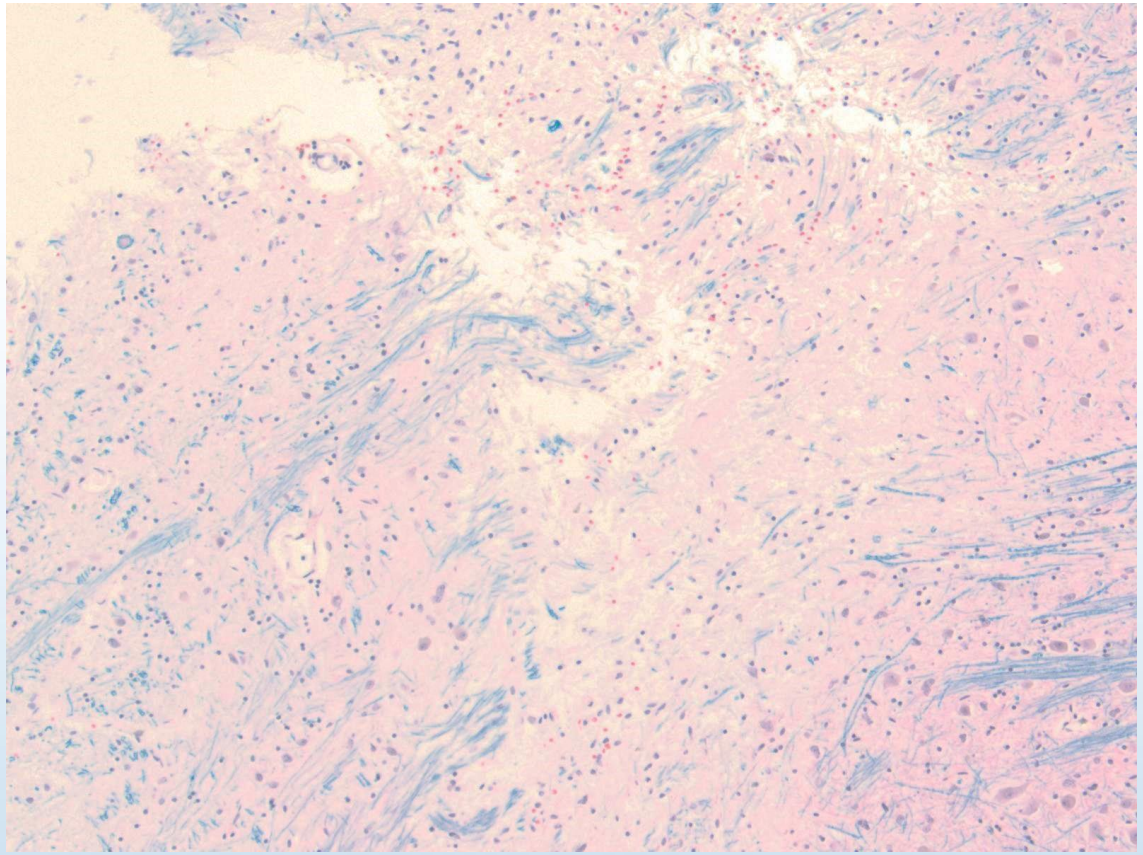


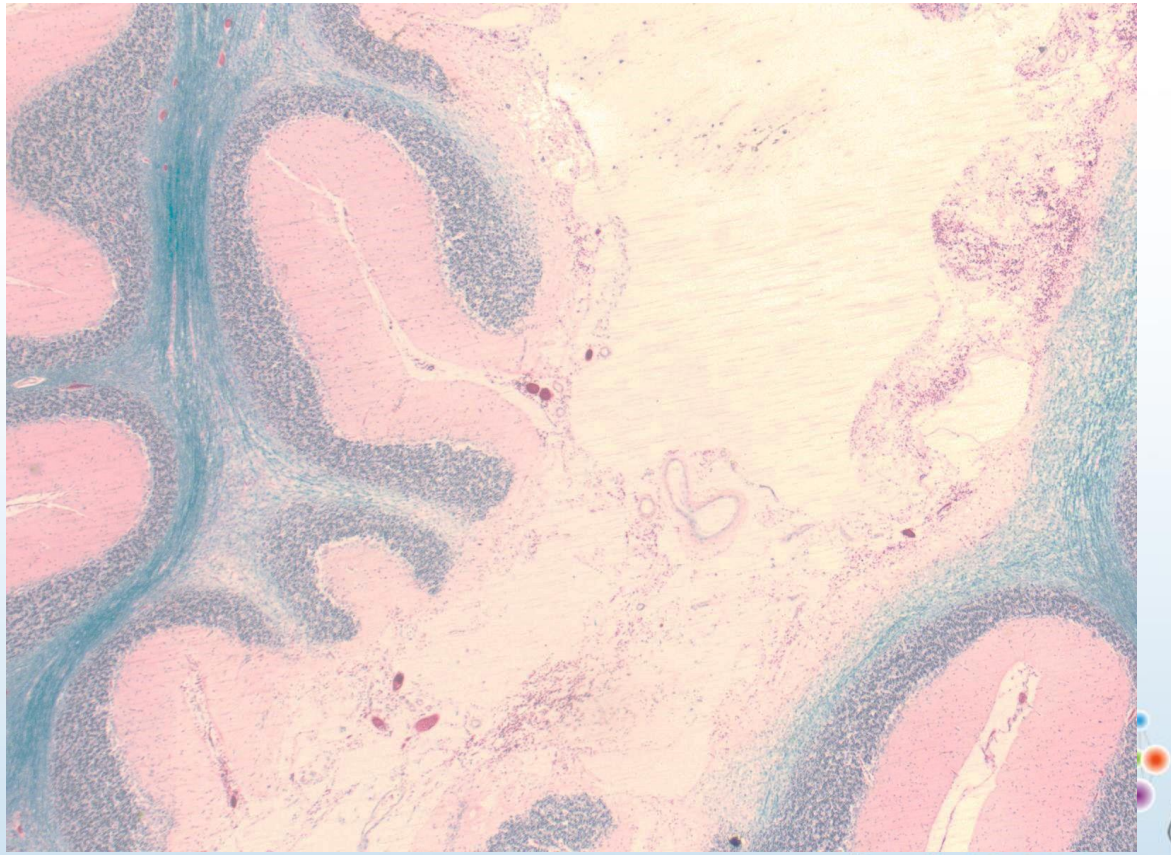
Chronic infarcts: right anterior caudate/claustrum



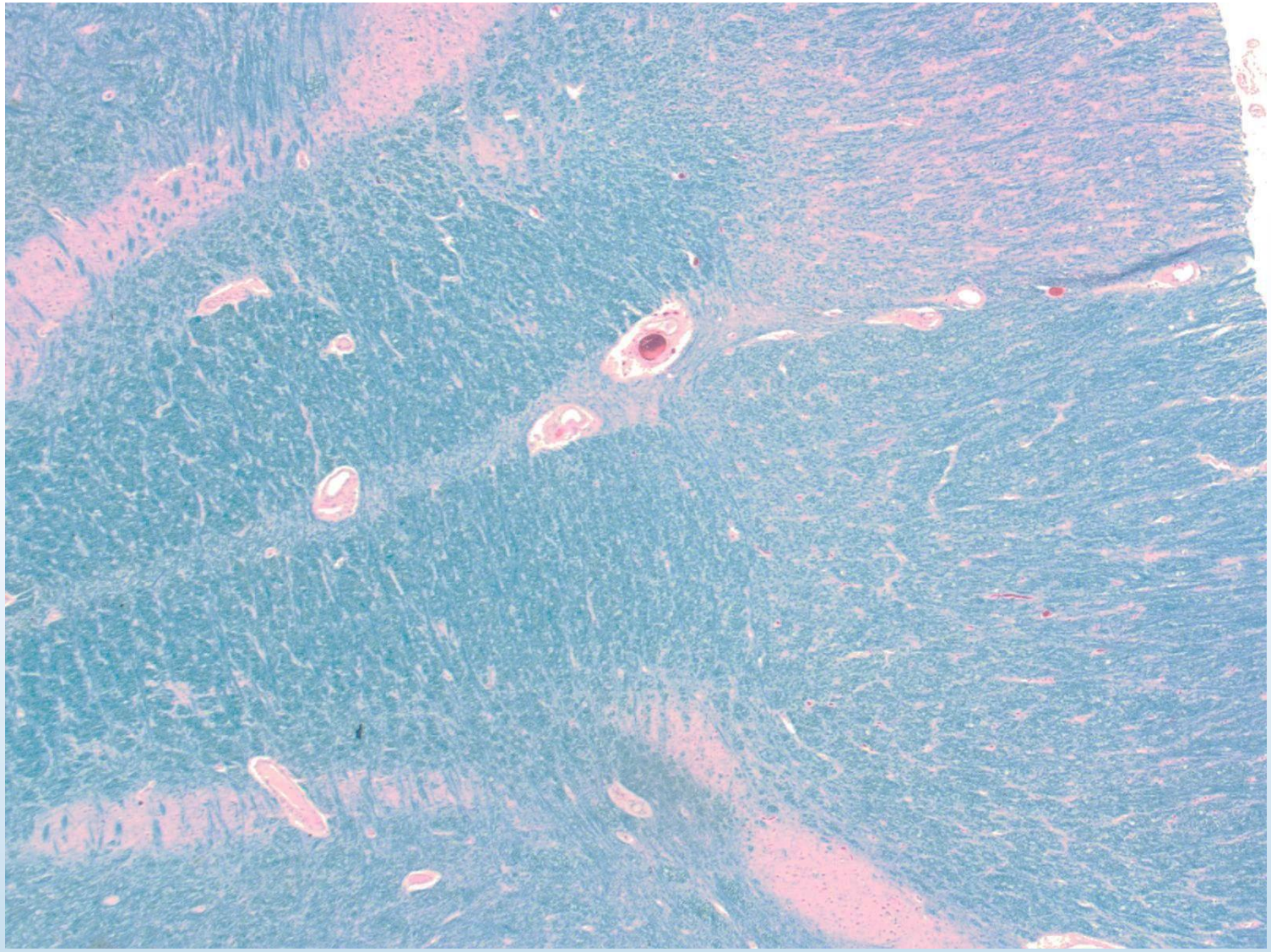


Chronic infarcts, basis pontis and right cerebellum

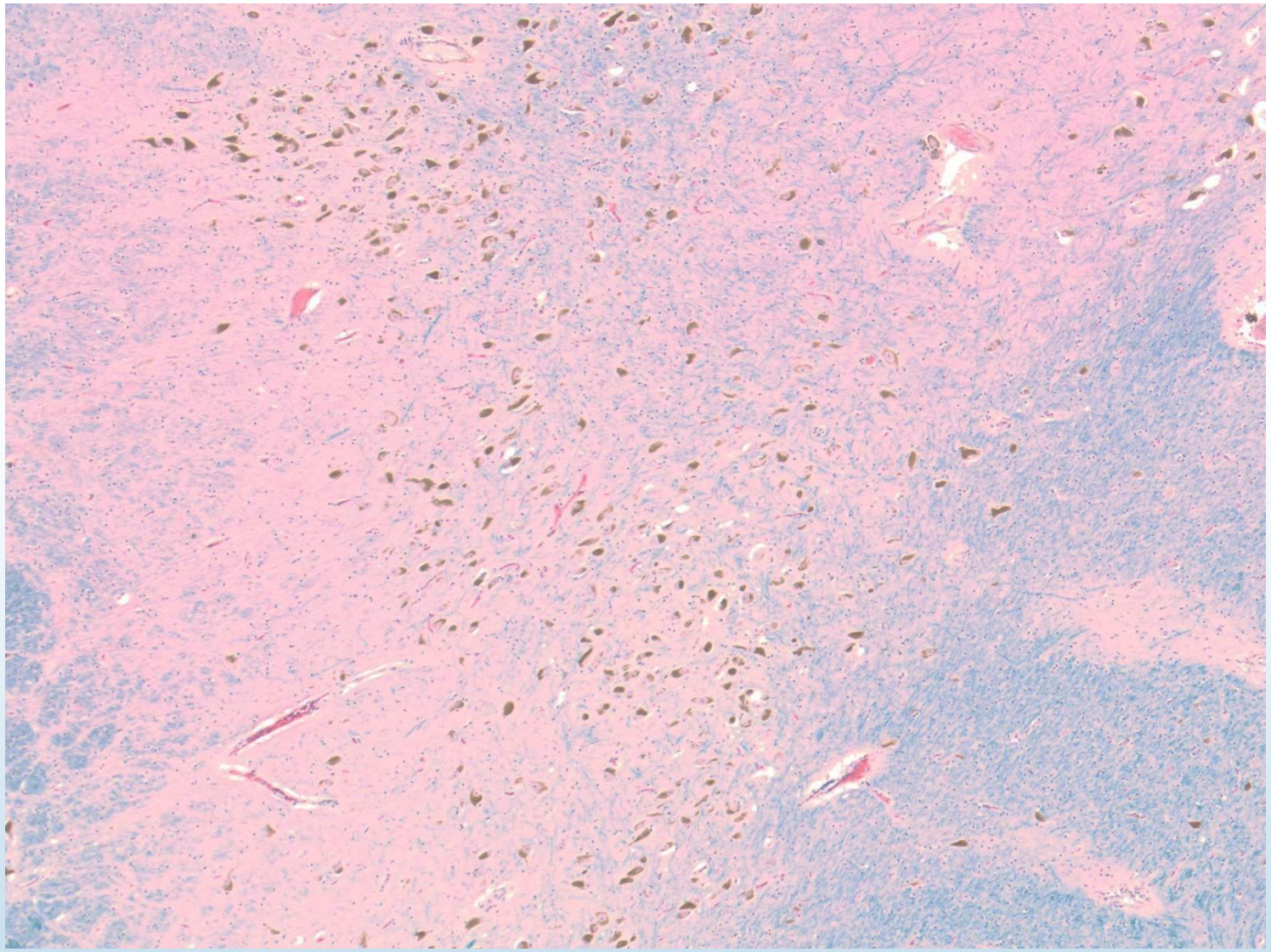




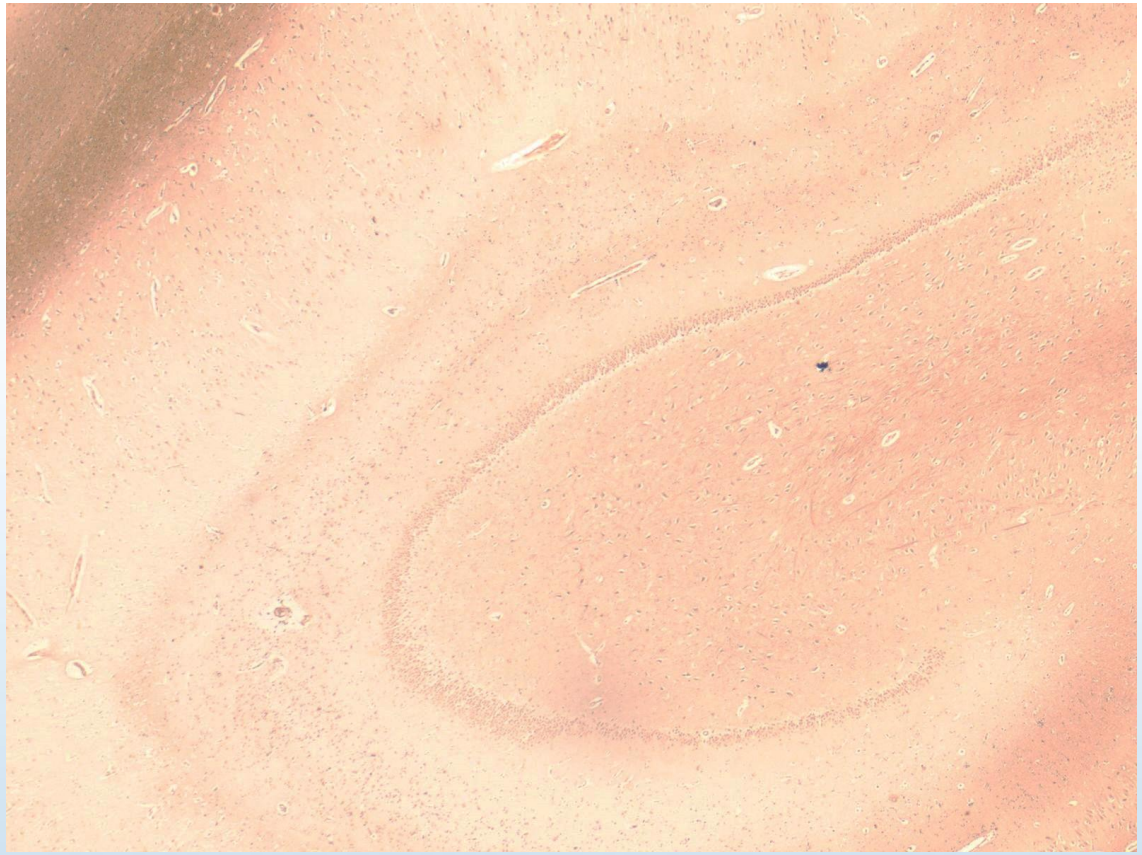
Wallerian degeneration, medulla

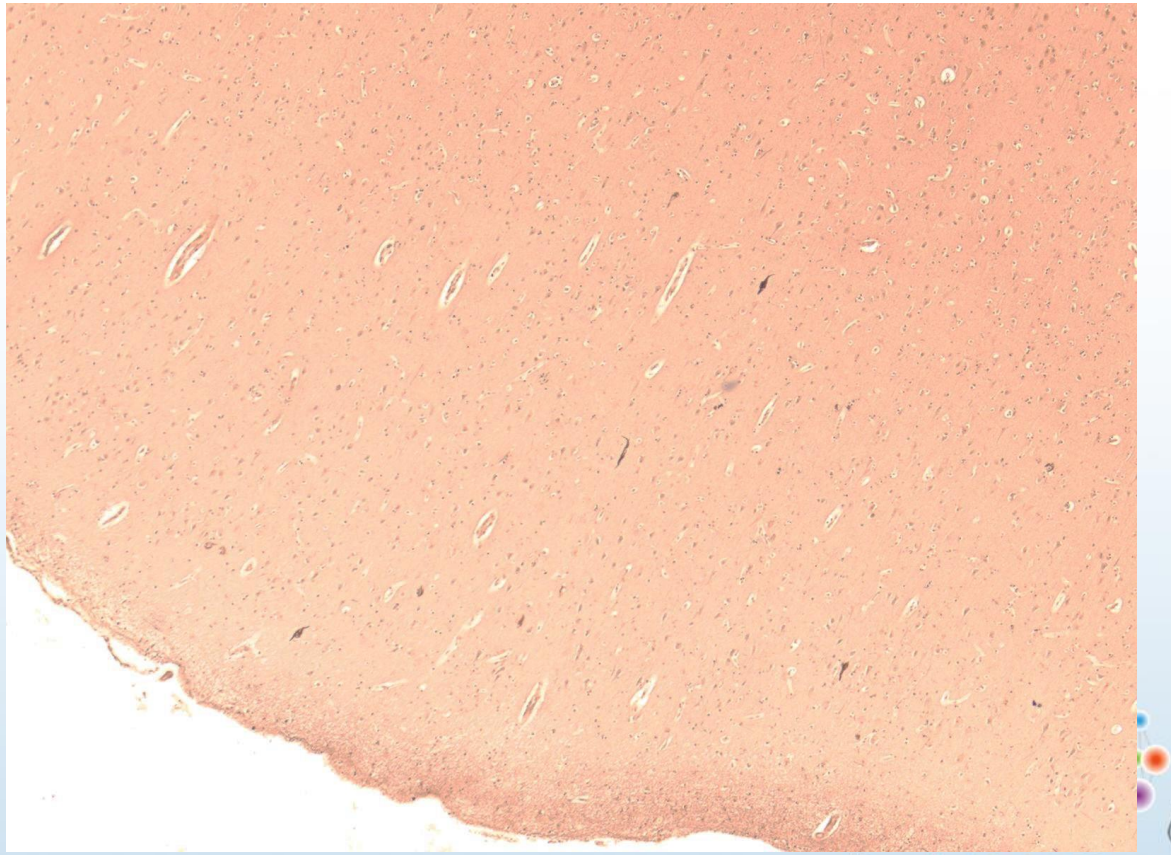


Substantia nigra (intact)



Hippocampus and medial temporal cortex, Bielschowsky stain—minimal pathology





Final Neuropathologic Diagnosis

- Traumatic brain injury, acute (clinical history of presumed fall)
- Cerebrovascular disease, extensive
- Clinical history of dementia; no evidence of significant neurodegenerative disease pathology

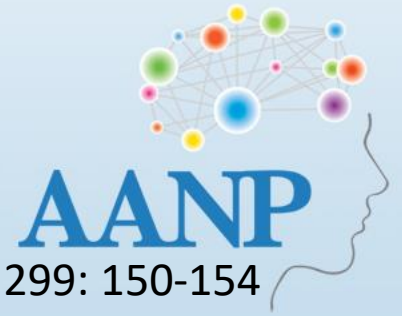
- (Presumed diagnosis: vascular dementia, likely multi-infarct dementia)

Vascular dementia

- Very common to have co-existing cerebrovascular disease in decedents with neurodegenerative diseases (e.g., Alzheimer disease, dementia with Lewy bodies), resulting in an exacerbation of cognitive dysfunction
- Uncommon to have pure cerebrovascular disease as the sole cause of dementia in the absence of a genetic mutation
- How common is “vascular dementia,” really?

Vascular dementia—one study

- 1,110 consecutive autopsies of elderly decedents with dementia (1994-2008)
- Frequency of diagnoses:
  - Alzheimer disease (AD): 44.1%
  - AD + small-vessel disease: 25.7%
  - **Vascular dementia (VaD): 10.8%**
  - AD + Lewy pathology: 9.6%
  - "Mixed dementia" (AD + VaD): 4.8%
  - Other degenerative disorders: 3.9%
  - Other disorders (post-traumatic, alcohol, etc.): 1.6%



Jellinger KA, Attems A, *J Neurol Sci* 2010; 299: 150-154

Vascular dementia—one study

- Frequency of morphologic subtypes of VaD (120 cases):
  - Subcortical arteriosclerotic encephalopathy: 49.1%
  - Multi-infarct encephalopathy: 38.3%
  - Strategic-infarct dementia: 9.2%
  - Severe cerebral amyloid angiopathy without major AD pathology: 3.6%
- General autopsy findings: signs of hypertension (92%), H/O diabetes/related lesions (61.3%), myocardial infarct (52%), "cardiac decompensation" (58%)
- Gradual decreased incidence with advancing age

Jellinger KA, Attems A, *J Neurol Sci* 2010; 299: 150-154

Vascular dementia—clinical features

- Motor and cognitive impairment: changes in gait, behavior, and mood
- Classically a “stepwise” neurologic decline
- Usually associated with vascular risk factors (hypertension, diabetes, hyperlipidemia, smoking, etc.)
- Incidence may be declining with more aggressive treatment of hypertension and other risk factors

Yachnis A, Rivera-Zengotita M (eds.). “High-Yield Pathology: Neuropathology,” pp. 276-7

Vascular dementia—subtypes

- Subcortical arteriosclerotic (leuko)encephalopathy or Binswanger disease
  - Executive dysfunction with cognitive impairment
  - Severe small-vessel disease with widespread white matter demyelination without frank necrosis or pronounced infarction
- Multi-infarct dementia: results from multiple strokes of various sizes in several locations
- Strategic-infarct dementia: well-placed subcortical infarcts that disrupt specific circuits leading to executive dysfunction and personality change/apathy with relatively small overall lesion volume
- Cerebral amyloid angiopathy: microvascular ischemic changes (rare)

Lowe J, Kalaria R, "Greenfield's Neuropathology, Ninth Edition," pp. 930-48
Yachnis A, Rivera-Zengotita M (eds.). "High-Yield Pathology: Neuropathology," pp. 276-7

Considering a diagnosis of “vascular dementia”

- Clinical history of dementia
- Widespread and/or well-placed cerebrovascular disease pathology
- No significant neurodegenerative disease pathology

- (In my experience, this trifecta is very rare)

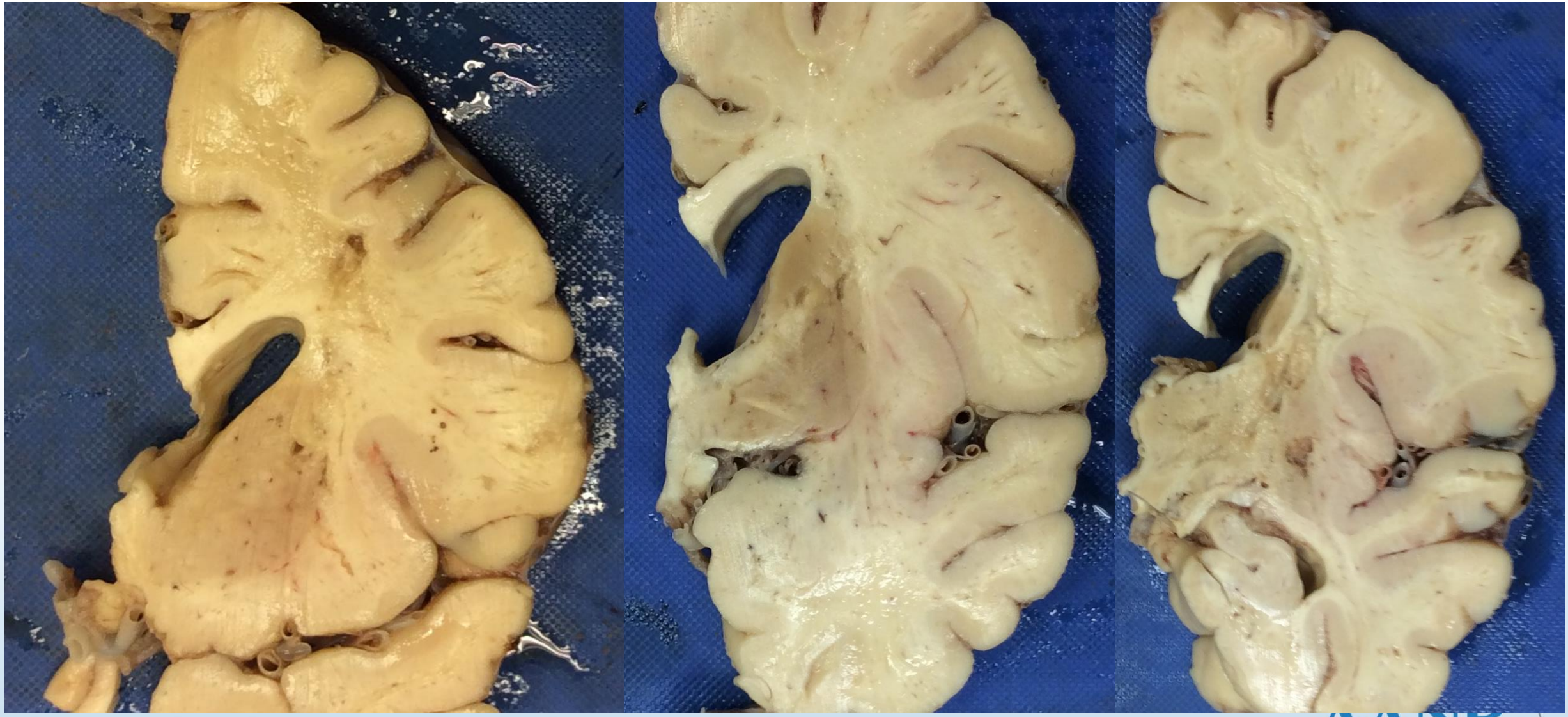
CASE #5

History

- 48-year-old man initially evaluated in the Memory Disorders Clinic on 2/13/2006
- Developed migraine in his 20's
- Had multiple ischemic episodes; first one in 1994 where he received a diagnosis of multiple sclerosis
- Subsequent episodes in April and May of 2001
- Had skin biopsy and was diagnosed with CADASIL
- MRI appearance also consistent with CADASIL

History

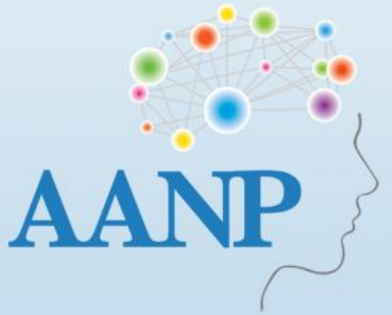
- Last outpatient clinical note is dated 6/29/2017
- Lived in a nursing facility with inability to walk; falling out of wheelchair, requiring a restraint
- Progressively hypophonic speech
- Progressive dementia
- Death in December 2018 at age 61



VIRTUAL SLIDE

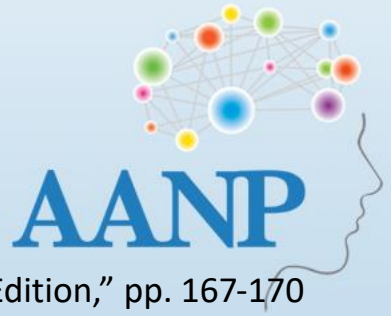
Final Neuropathologic Diagnosis

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
  - Clinical history of CADASIL diagnosed by skin biopsy in May 2001
  - Lacunar infarcts: corona radiata, putamen, and thalamus, chronic
  - Arteriolosclerosis, diffuse, severe, with widespread cribriform change
  - Multiple foci of white matter pallor
  - Wallerian degeneration, corticospinal tract



CADASIL

- First described in 1955 as “familial Binswanger disease”
- Linked to chromosome 19 in 1993
- *NOTCH3* gene and its protein identified in 1996
- More than 700 families worldwide
- Estimated prevalence of 4-5 per 100,000



Kalaria R, Ferrer I, Love S, “Greenfield’s Neuropathology, Ninth Edition,” pp. 167-170

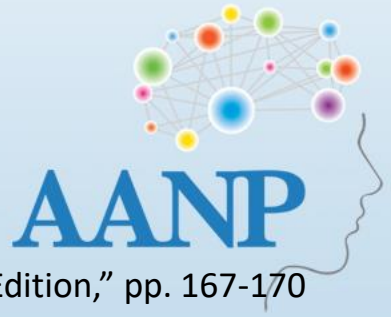
CADASIL—clinical features

- Migraine with aura, severe (some with hemiparesis)
- Recurrent ischemic strokes
- Psychiatric symptoms
- Cognitive decline/dementia
- Seizures may be seen in late-stage disease
- Treatment is symptomatic/supportive

Kalaria R, Ferrer I, Love S, "Greenfield's Neuropathology, Ninth Edition," pp. 167-170
Yachnis A, Rivera-Zengotita M (eds.). "High-Yield Pathology: Neuropathology," pp. 58-9

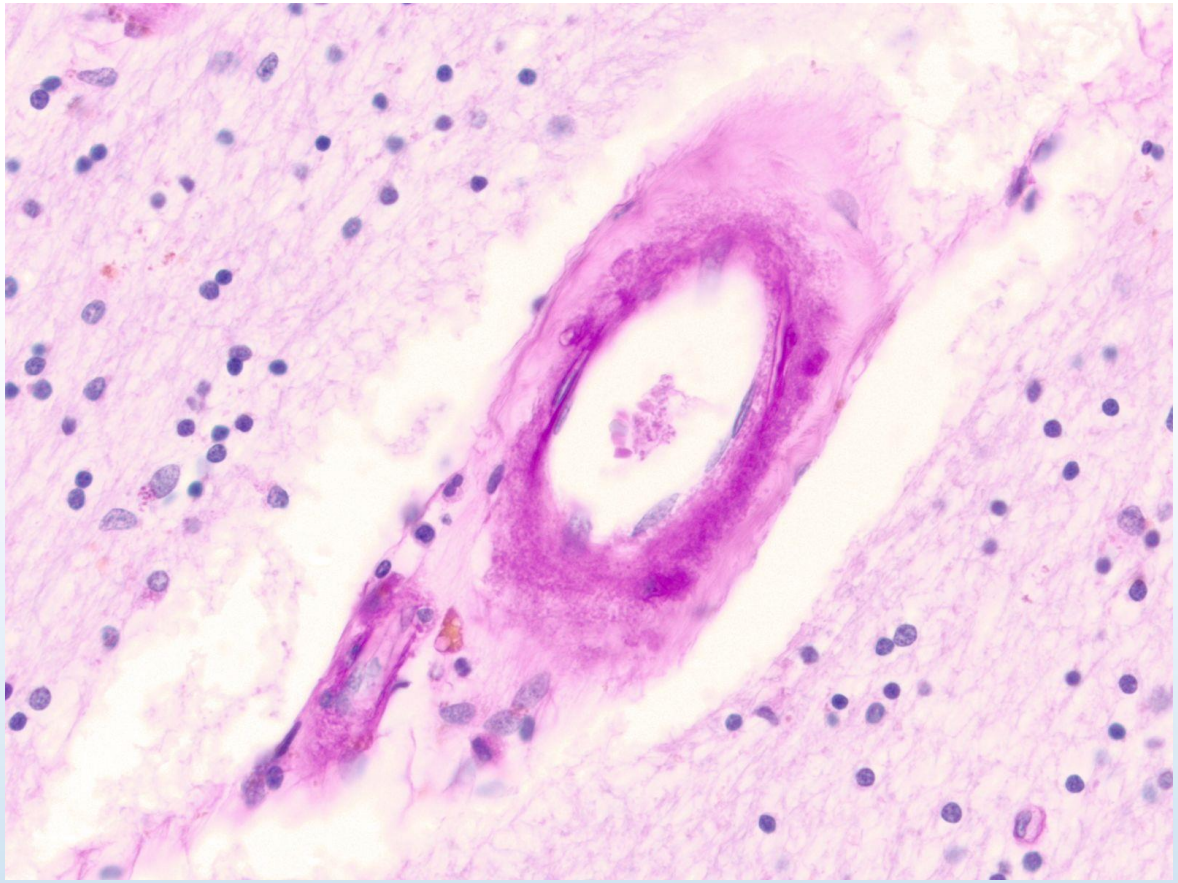
CADASIL—pathology

- Non-arteriosclerotic, non-amyloid arteriopathy
- Affects small- and medium-sized arteries
  - White matter
  - Leptomeninges
- Skin, skeletal muscle, and peripheral nerves also involved
- Degeneration of vascular smooth muscle cells
  - PAS-positive granules in tunica media
  - Granular osmiophilic material on electron microscopy
- Basal ganglia/thalamus/brainstem infarcts also seen

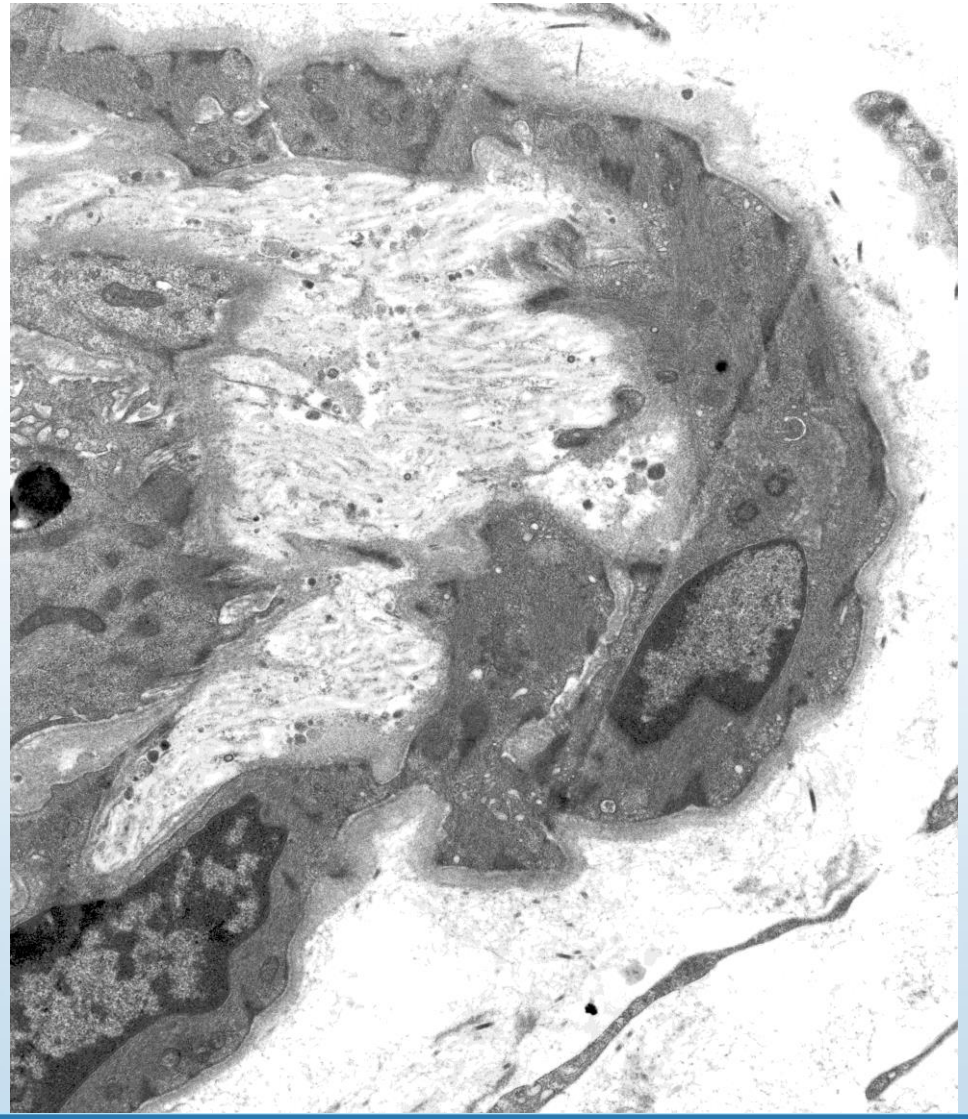


Kalaria R, Ferrer I, Love S, "Greenfield's Neuropathology, Ninth Edition," pp. 167-170

CADASIL—PAS stain (this autopsy)



Electron microscopy—2008 skin biopsy



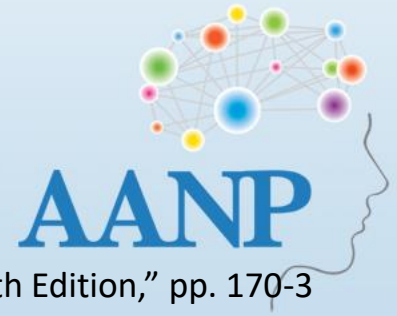
CADASIL—genetics

- Autosomal dominant
- *NOTCH3* gene on chromosome 19p13
- Functions in stem cell renewal, differentiation, proliferation, and apoptosis; required for survival and normal function of vascular smooth muscle cells
- Vast majority of abnormalities are missense point mutations
- Pathogenesis not entirely clear

Kalaria R, Ferrer I, Love S, "Greenfield's Neuropathology, Ninth Edition," pp. 167-170
Yachnis A, Rivera-Zengotita M (eds.). "High-Yield Pathology: Neuropathology," pp. 58-9

Other rare, inherited, non-amyloid vascular disorders

- CARASIL/Maeda syndrome
  - Multiple infarcts with cognitive impairment
  - Orthopedic manifestations and alopecia
  - Nonsense/missense mutations of *HTRA-1* on chromosome 10q
- Retinal vasculopathies with cerebral leukodystrophy
  - Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS); cerebroretinal vasculopathy (CRV); and hereditary vascular retinopathy (HVR)
  - Central visual loss with brain infarcts and cognitive impairment
  - Mutations in *TREX1* gene on chromosome 3



Kalaria R, Ferrer I, Love S, "Greenfield's Neuropathology, Ninth Edition," pp. 170-3

Q&A