Diagnostic Slide Session 2016
Case 5

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MASSACHUSETTS GENERAL HOSPITAL PATHOLOGY

Advancing Diagnosis and Discovery

HARVARD MEDICAL SCHOOL

Disclosures

- **none**

A 44 year-old man admitted to an OSH following a fall

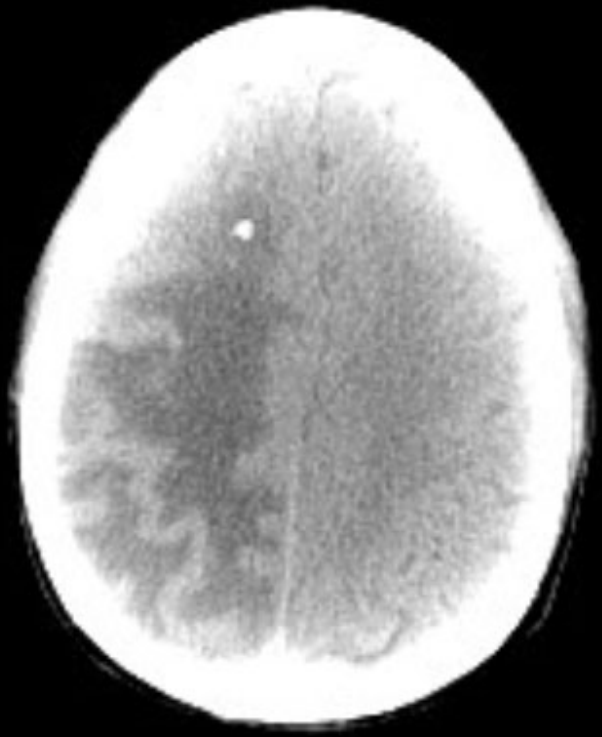
- One year of progressive memory loss, malaise, intermittent confusion, headache, and visual loss
- Past medical history:
  - Hypertension
  - Posterior uveitis with retinal vasculitis and macular degeneration
    - Treated with numerous immunosuppressive drugs, intravitreal steroids, and bevacizumab
  - Chronic progressive kidney disease, Stage 4
    - s/p 2 biopsies 2 & 4 years previously (results unavailable)

A 44 year-old man admitted to an OSH following a fall

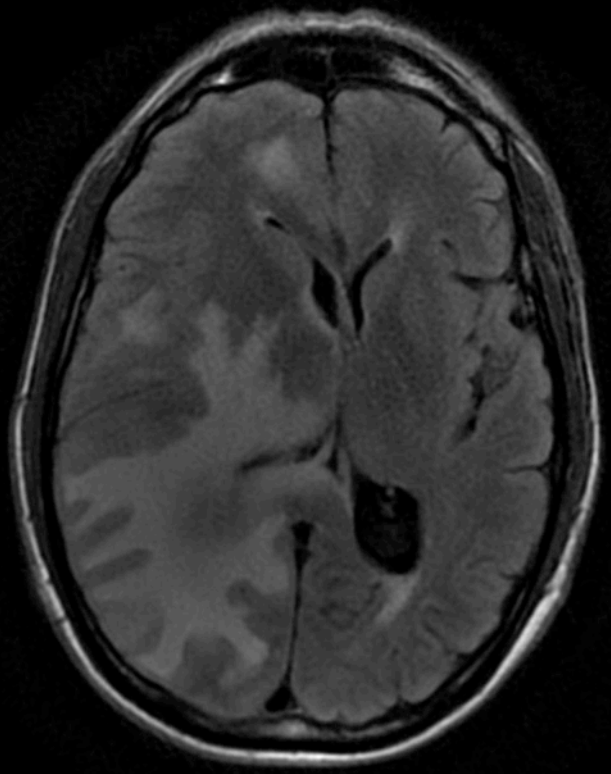
- Labs:
  - CSF MBP: 10.6
  - CSF IgG: Mildly elevated
  - JC Virus, flow cytometry, VDRL within normal limits
  - “immunologic and vasculitic workup negative”

A 44 year-old man admitted to an OSH following a fall

CT

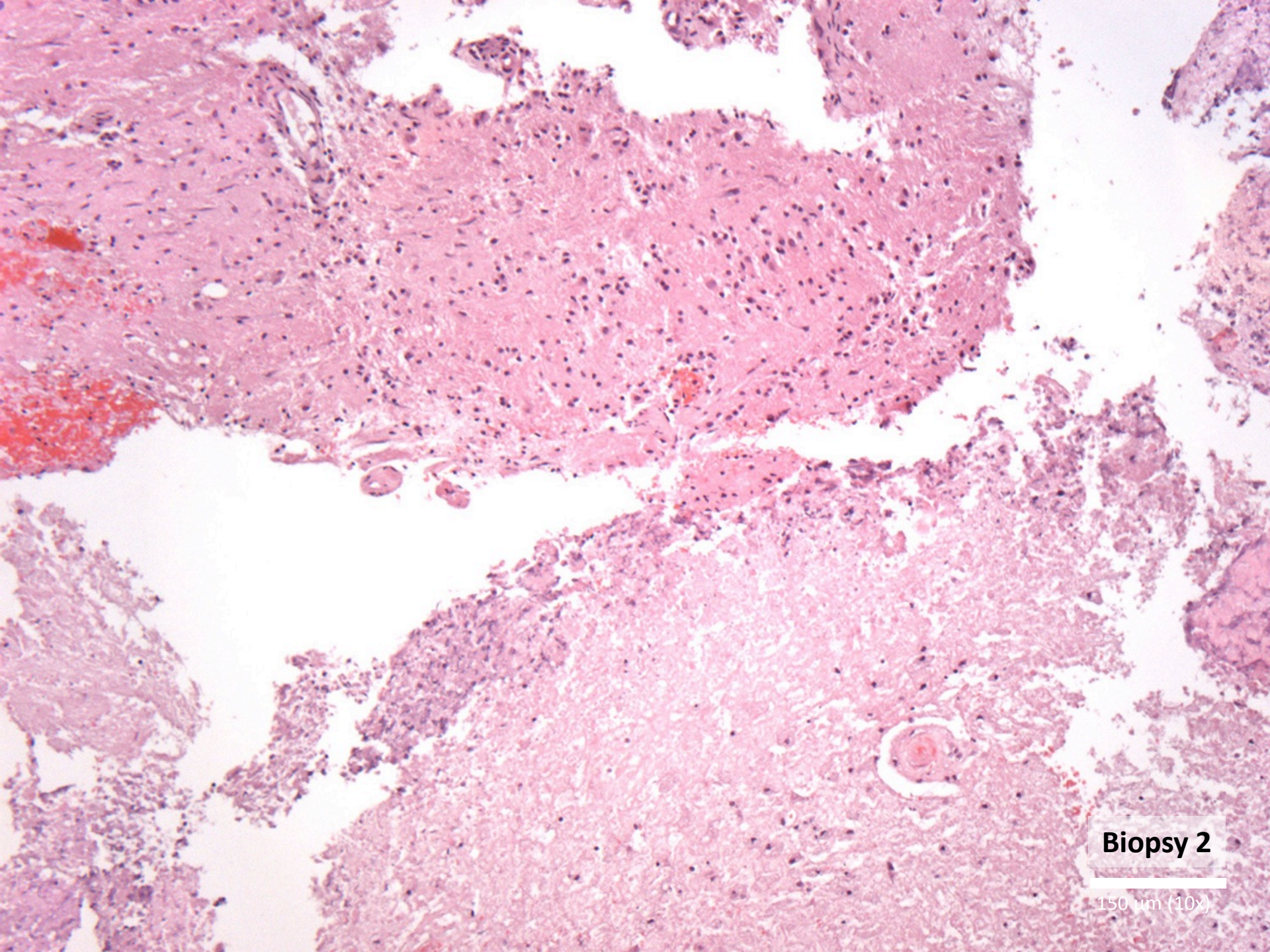


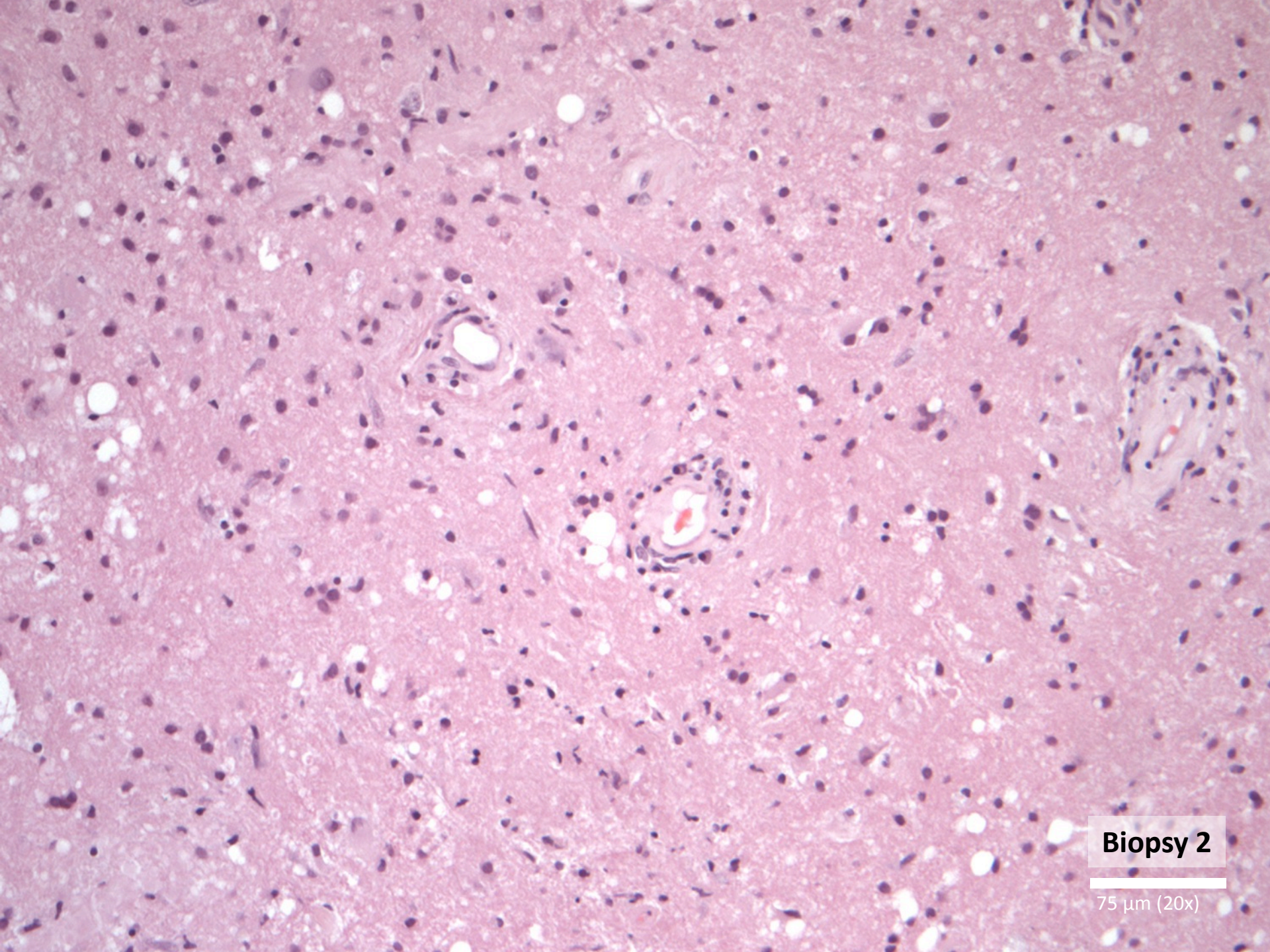
MRI - FLAIR

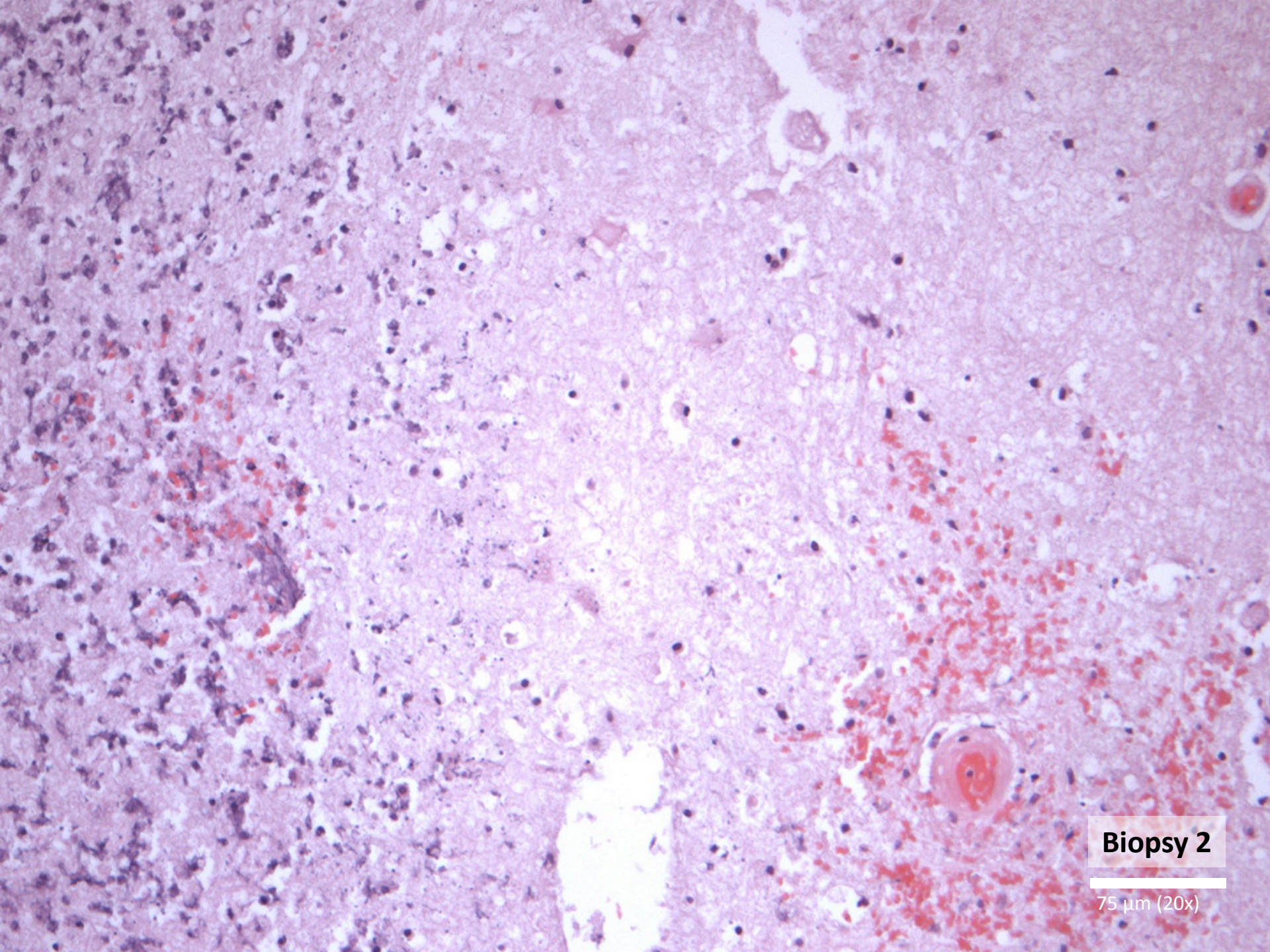


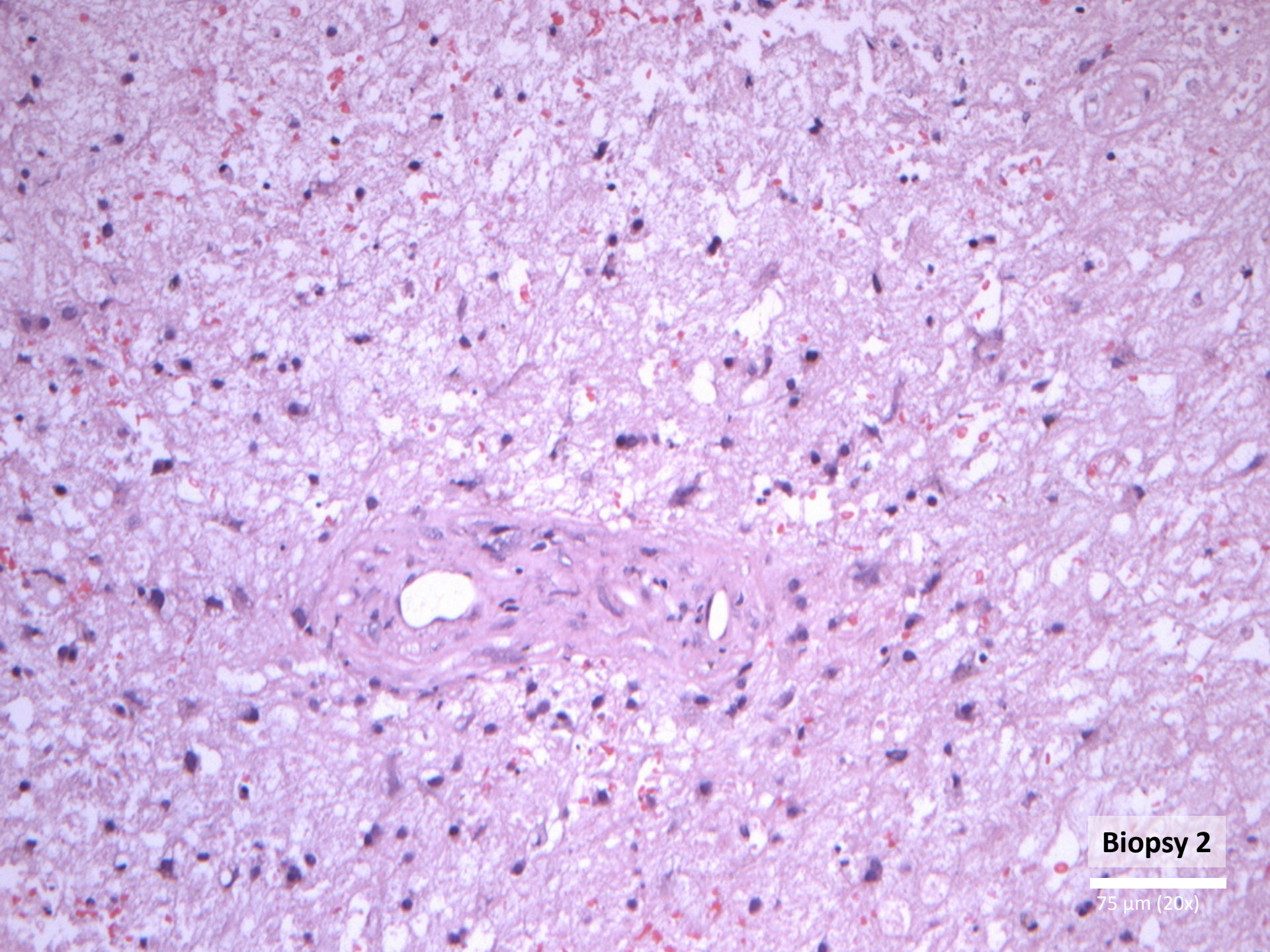
A 44 year-old man admitted to an OSH following a fall

- Clinical differential diagnosis:
  - Infectious, TB, syphilis, viral, toxoplasmosis, sarcoid, vasculitis, neoplastic, demyelination (PML), Behçet's disease.
- Brain biopsy of right parietal lesion:
  - 2 biopsies performed over the following two weeks
  - Second biopsy provided for DSS

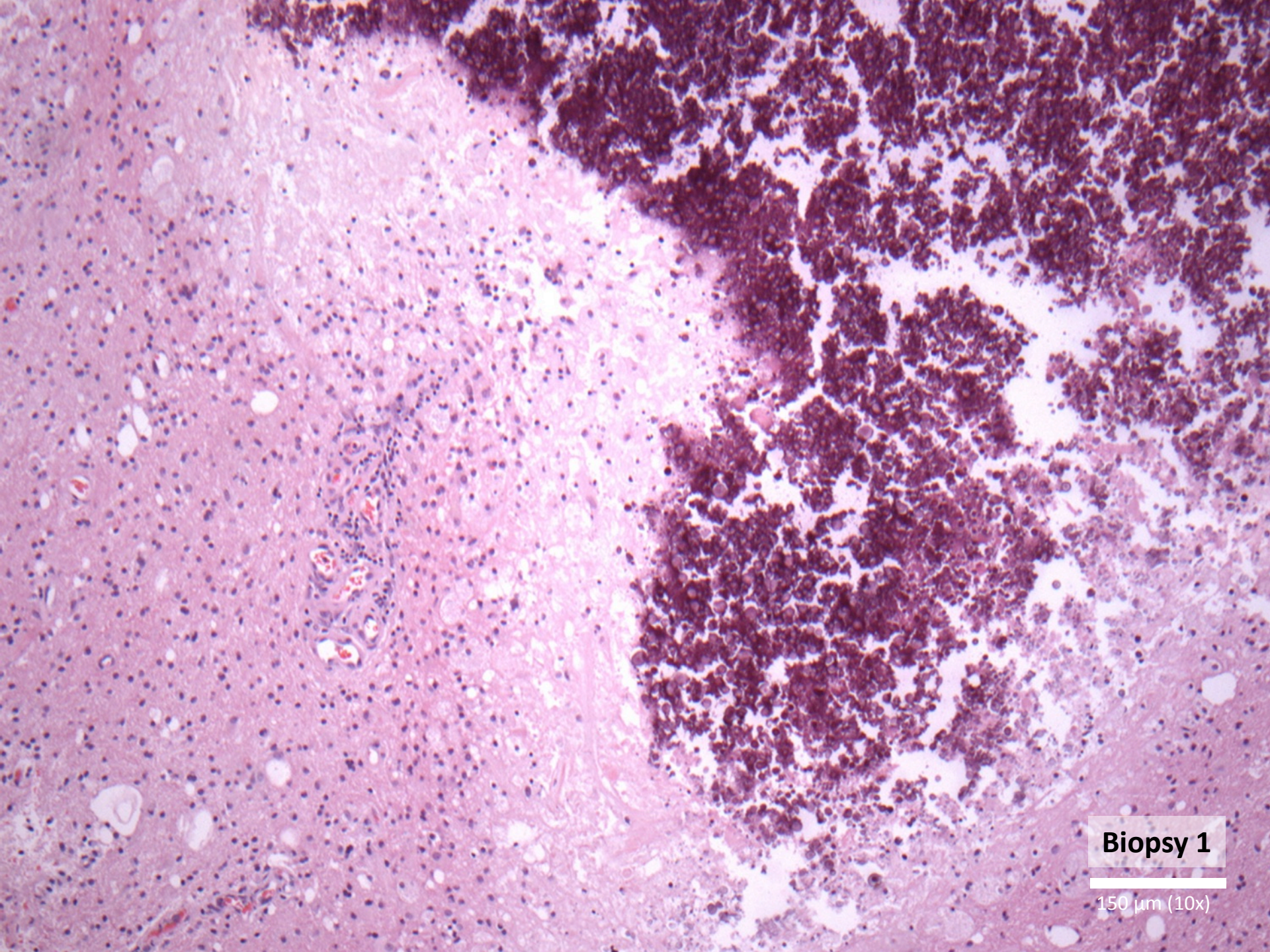

Biopsy 2
150 µm (10x)

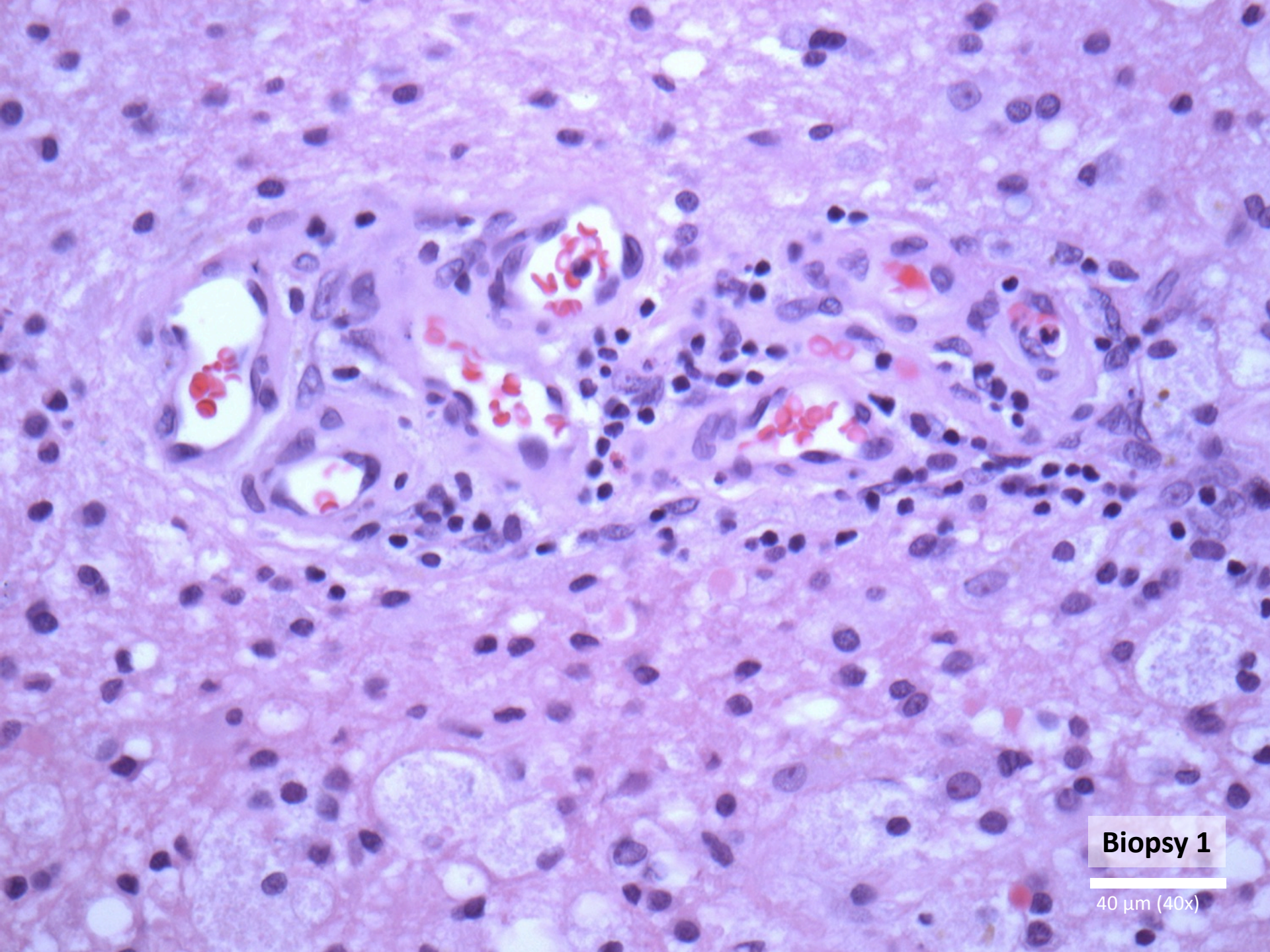

Biopsy 2
75 µm (20x)


Biopsy 2
75 µm (20x)

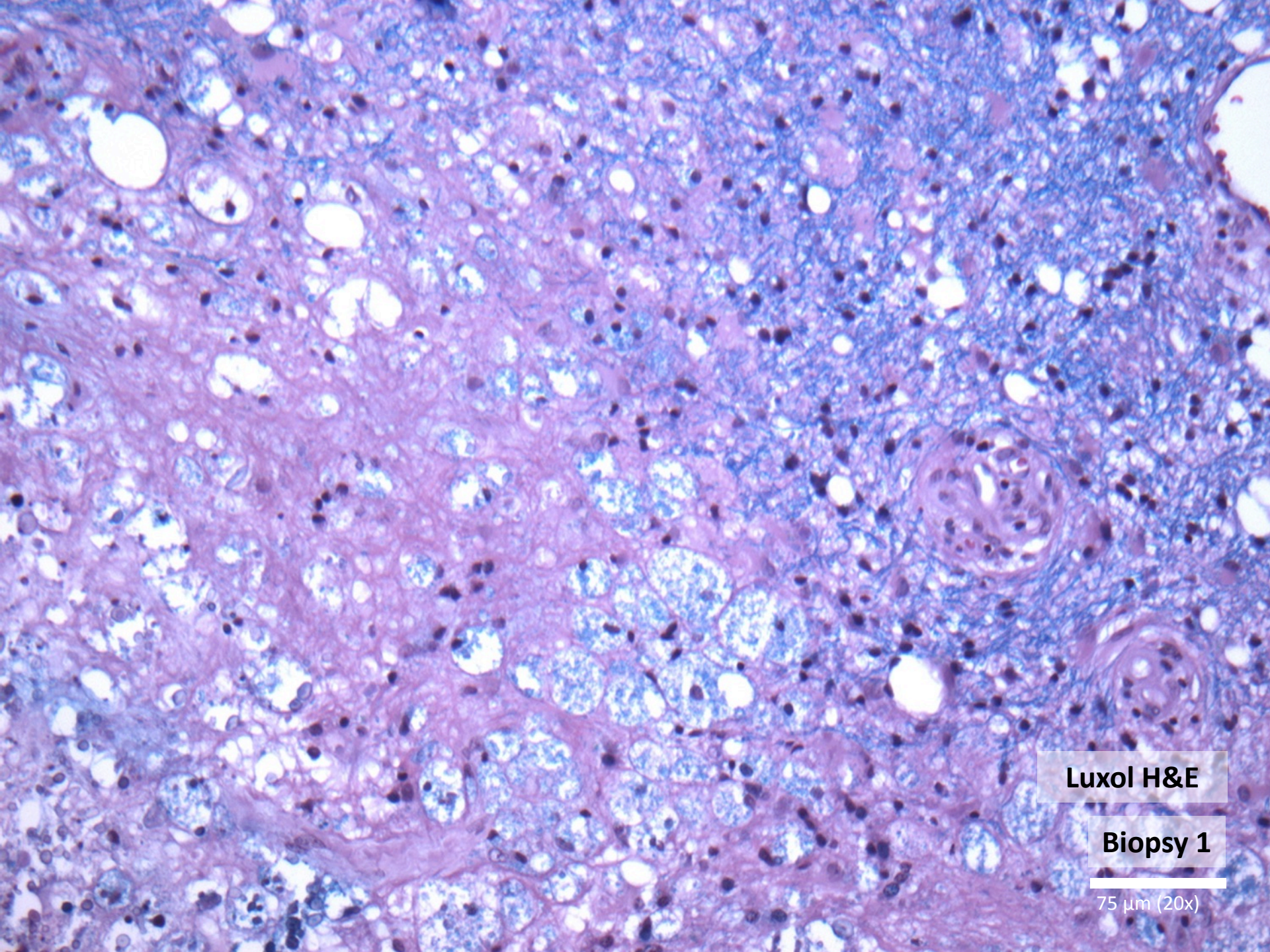

Biopsy 2
75 µm (20x)

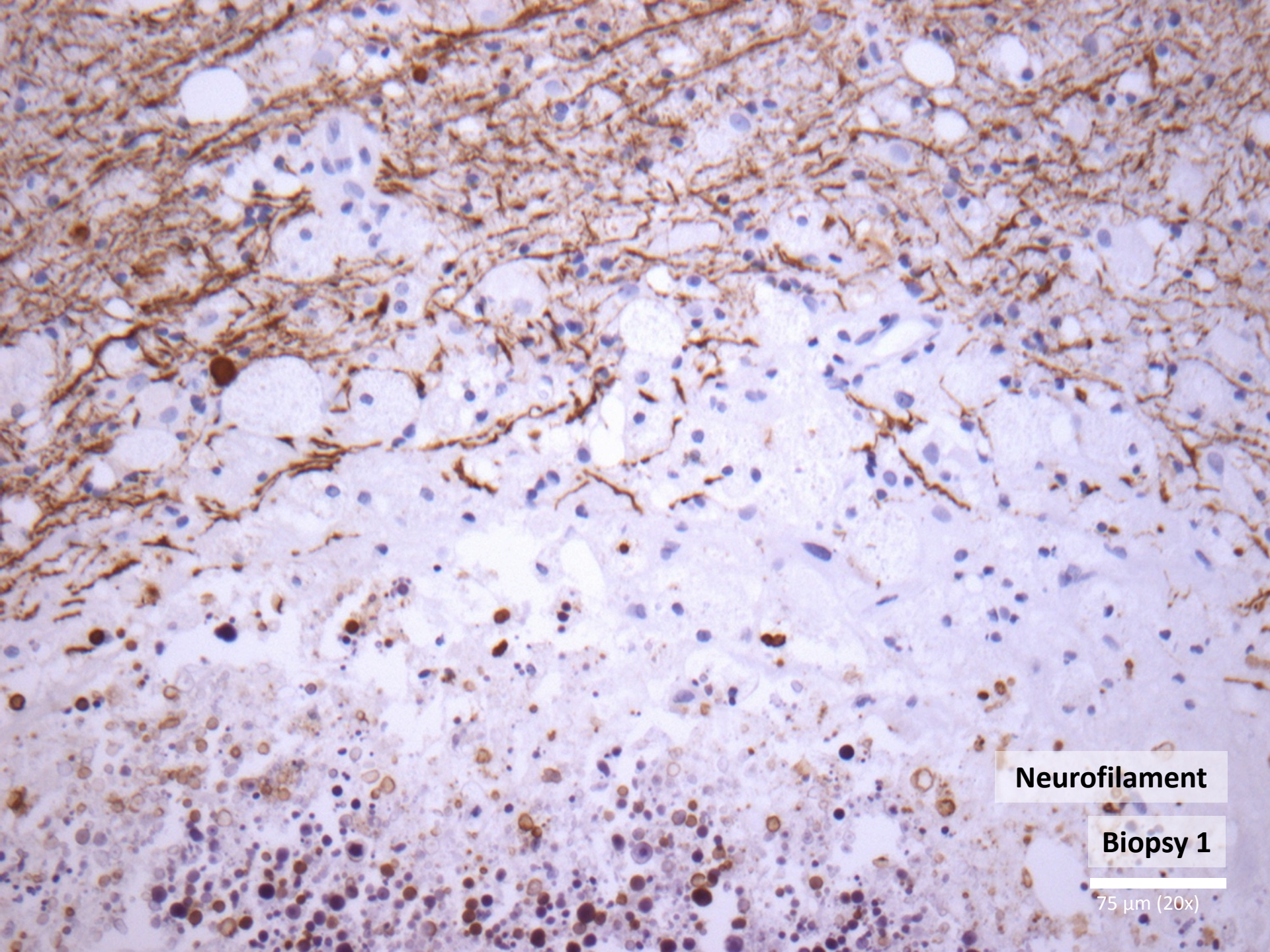
First biopsy

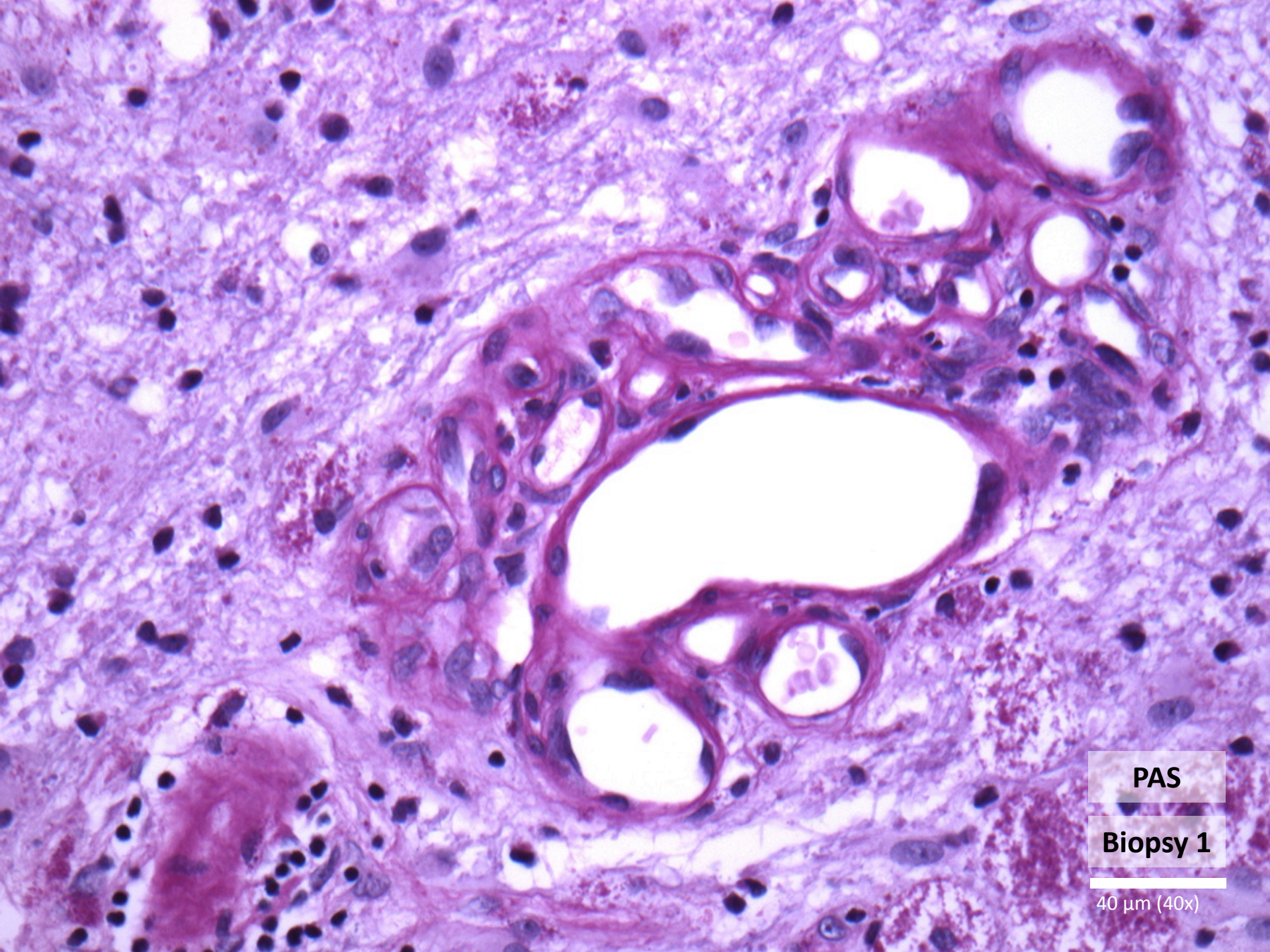

Biopsy 1
150 µm (10x)

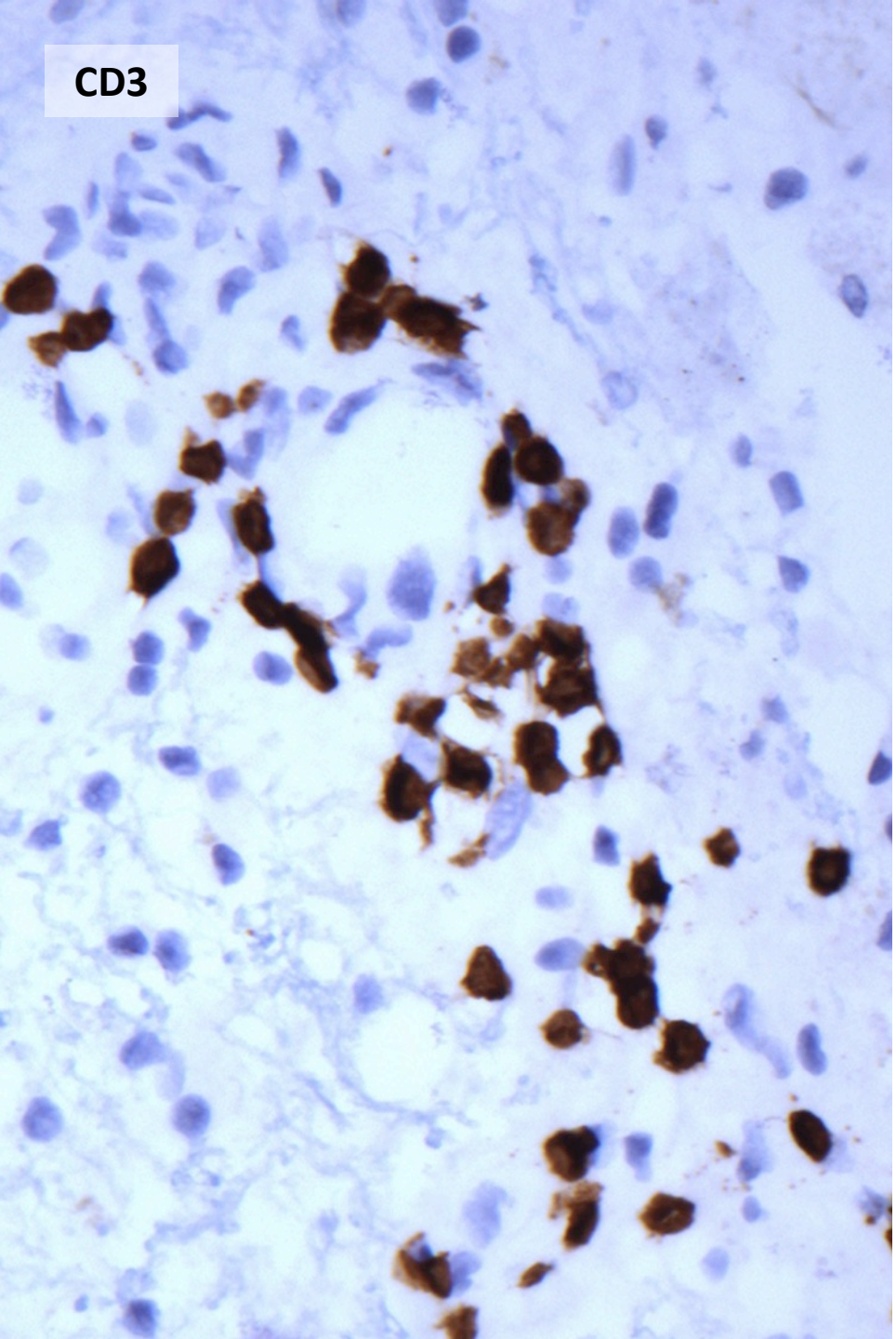

Biopsy 1
40 µm (40x)

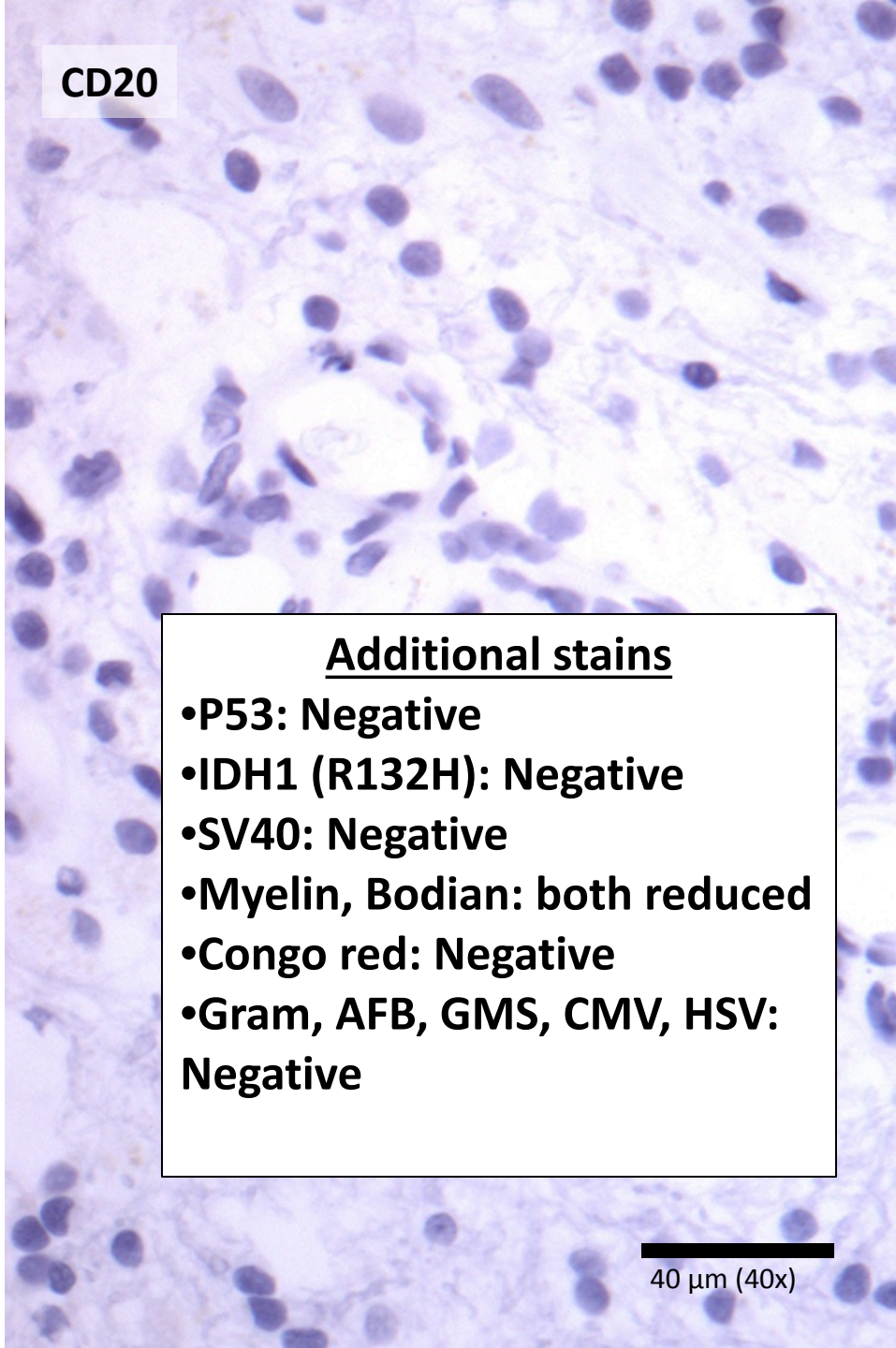
Diagnosis?


Luxol H&E
Biopsy 1
75 µm (20x)


Neurofilament
Biopsy 1
75 µm (20x)


PAS
Biopsy 1
40 µm (40x)


CD3


CD20
Additional stains
•P53: Negative
•IDH1 (R132H): Negative
•SV40: Negative
•Myelin, Bodian: both reduced
•Congo red: Negative
•Gram, AFB, GMS, CMV, HSV: Negative
40 µm (40x)

Descriptive final diagnosis

1. **Focal white matter necrosis with white matter calcification**

2. **Focal white matter necrosis and abnormal vessels in white matter**

Final Diagnosis

These findings, in the setting of retinopathy and renal dysfunction, are suggestive of retinal vasculopathy with cerebral leukodystrophy (RVCL)

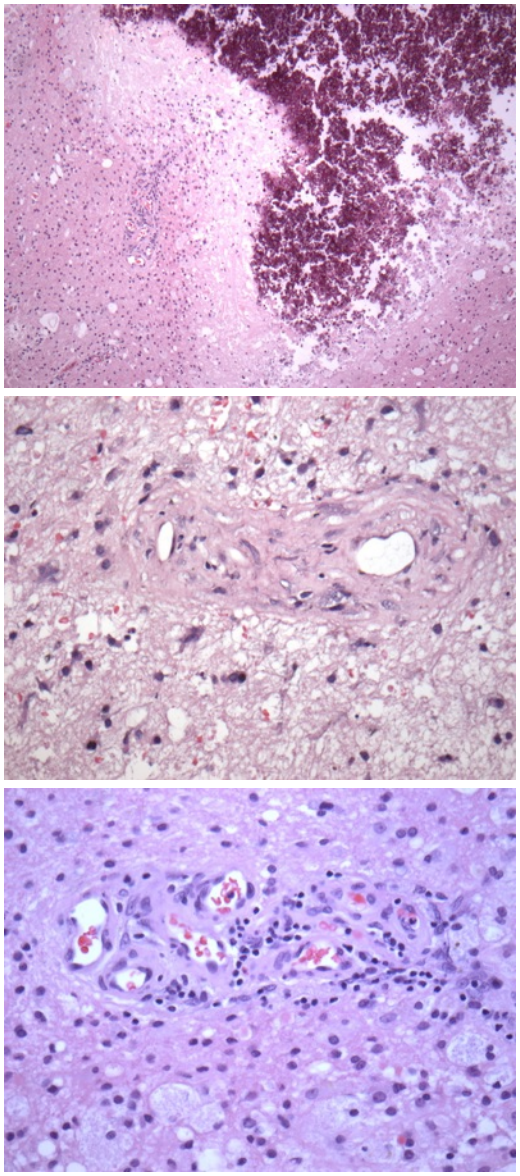
(Kolar et al., Brain Pathology 2014, DiFrancesco et al., Neurol. Sci. 2015)

Retinal vasculopathy with cerebral leukodystrophy (RVCL)

- Autosomal dominant, 100% penetrance
- Heterozygous frameshift mutations in TREX-1
- Presents in 30s-40s with visual changes, headache, +/- focal neurologic deficits
- Vasculopathy of white matter, retina and other organs (kidney, liver)

RVCL pathologic features

- White matter ischemia, necrosis, and dystrophic calcification
- Thickened hyalinized vessels
- Fibrinoid vascular necrosis
- Vascular telangiectasias
- Multi-laminated basement membranes on electron microscopy



(Kolar et al., Brain Pathology 2014)

Additional history was obtained

Family History:

- Father died at age 36 from Hodgkin's lymphoma
- Paternal uncle died in his early 40s from an unclear disease with renal dysfunction

TREX1 sequencing

- Novel C-terminal frameshift mutation
- c.830-833dupAGGA

Followup

RVCL disease course:

- Poor prognosis
- Limited therapeutic options
  - Glucocorticoids
- Death within 5-10 years of symptom onset

This patient:

- Trial of experimental immunosuppressive therapies
- Discontinued due to opportunistic infections
- Progressive renal disease requiring hemodialysis
- Transitioned to hospice care 13 months after first presentation
- He died 1 month later at age 45

References:

- Kolar GR, Kothari PH, Khanlou N, Jen JC, Schmidt RE, Vinters HV. Neuropathology and genetics of cerebroretinal vasculopathies. Brain Pathol. 2014 Sep;24(5):510-8.

- DiFrancesco JC, Novara F, Zuffardi O, et al. TREX1 C-terminal frameshift mutations in the systemic variant of retinal vasculopathy with cerebral leukodystrophy. Neurol Sci 2015;36:323– 330.

- Vodopivec I, Oakley DH, Perugino CA, Venna N, Hedley-Whyte ET, Stone JH. *A 44-year-old man with eye, kidney, and brain dysfunction*. Ann Neurol. 2016 Apr;79(4):507-19.