DSS Case #6

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Disclosures

"The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army and Department of Defense or the U.S. Government.“

We have no relevant financial disclosures.

Clinical History

- CC: 20 y/o male presented for EGD due to dysphagia and tooth pain
- PMH: Hypertension, obstructive sleep apnea, and a congenital musculoskeletal disorder
- Airway instability with subsequent desaturation during EGD
- Resussitative efforts were unsuccessful

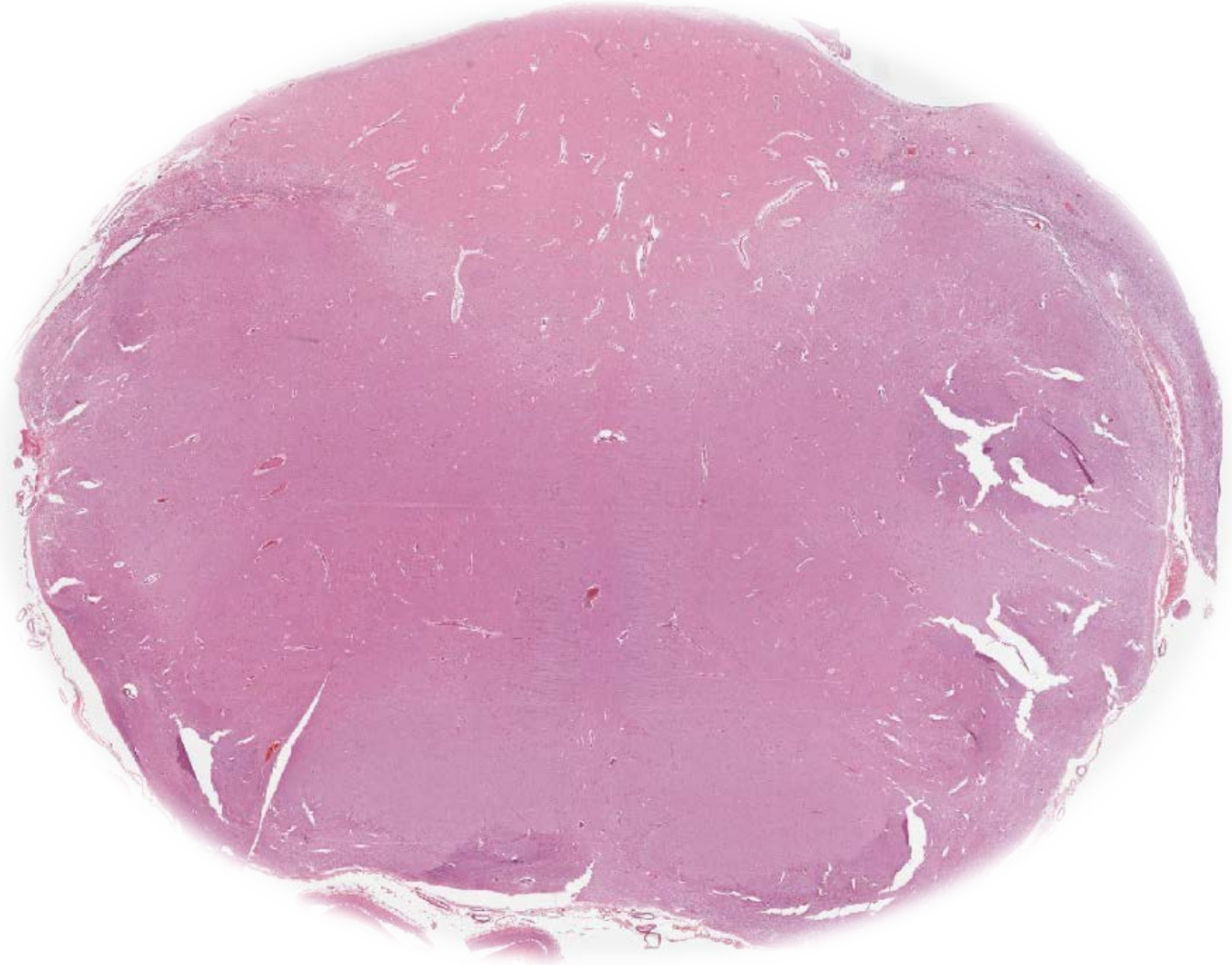
Autopsy Findings:

- Thin male, short stature, 75 lbs weight
- Scoliosis, pes planus, and asymmetrical muscular atrophy

Gross Brain Findings:

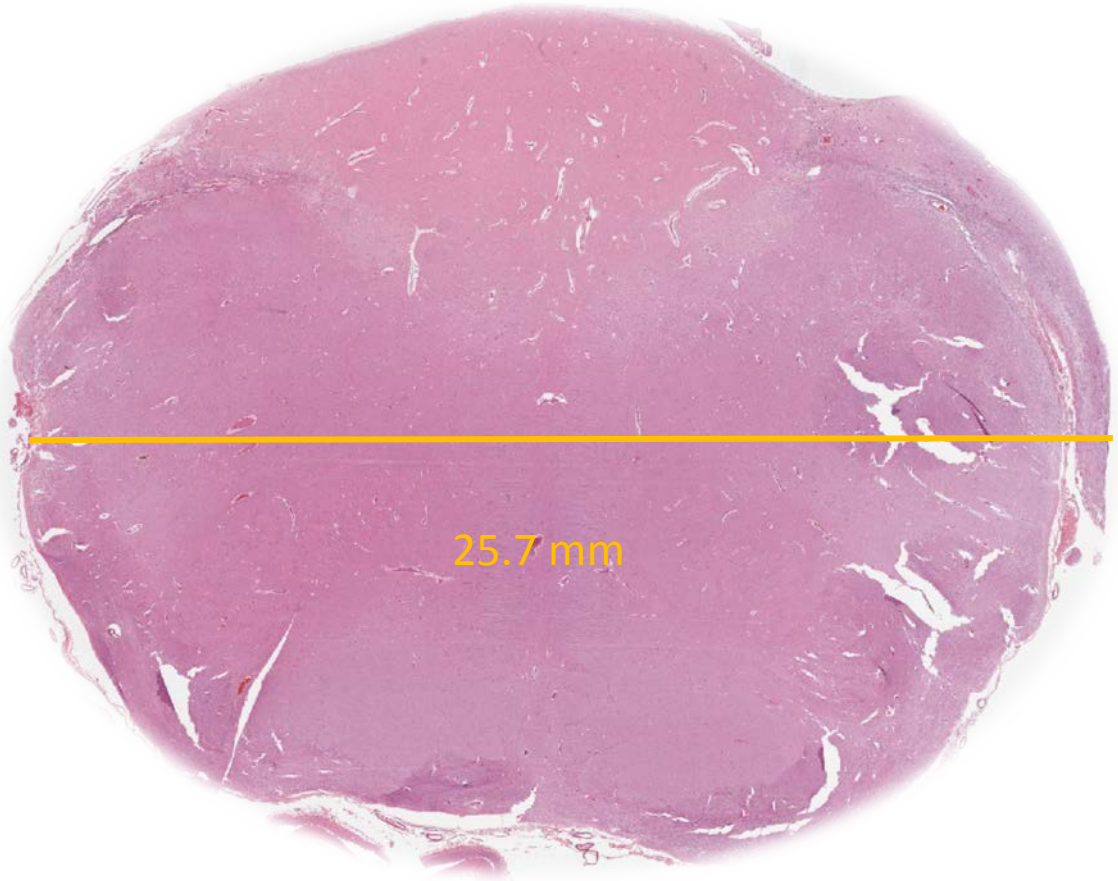
- Brain: 1,560 grams
- Enlarged brainstem with markedly stenotic aqueduct
- Ovoid medulla
- Internal architecture of the brainstem appeared distorted
- The dentate nuclei of the cerebellum were difficult to delineate grossly
- Obliteration of the fourth ventricle

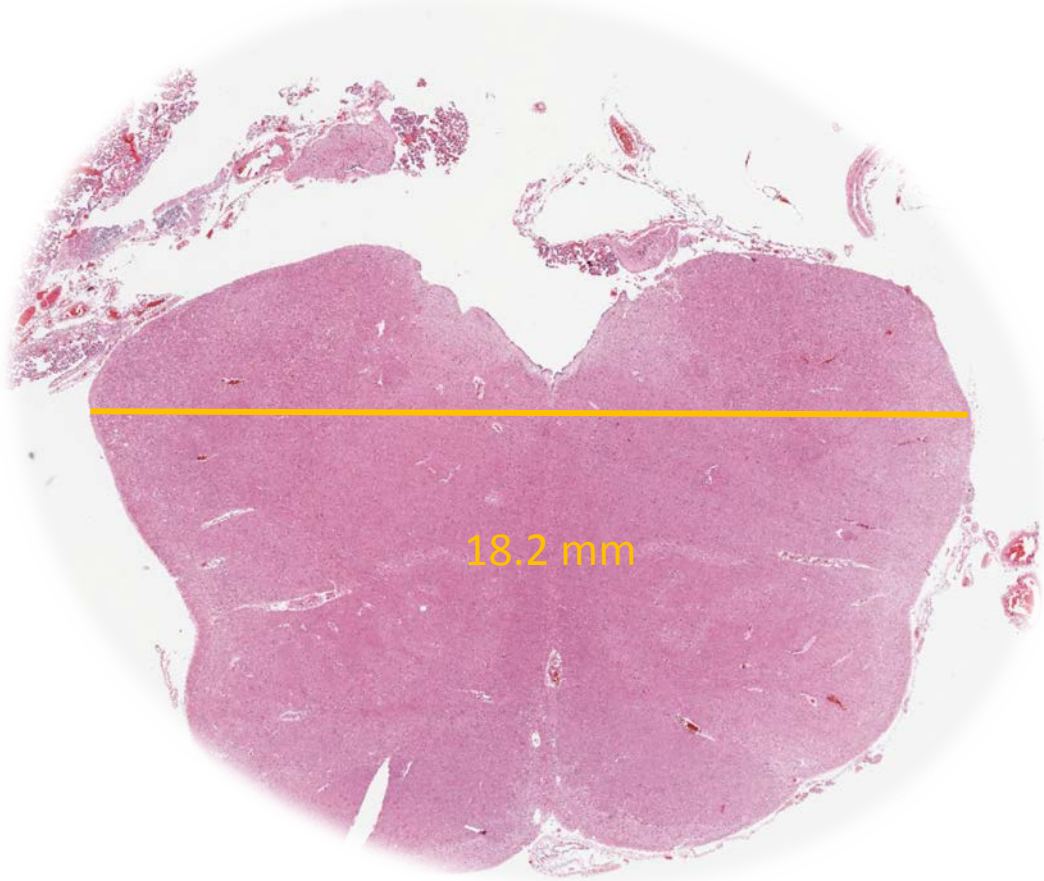
Cross section of medulla

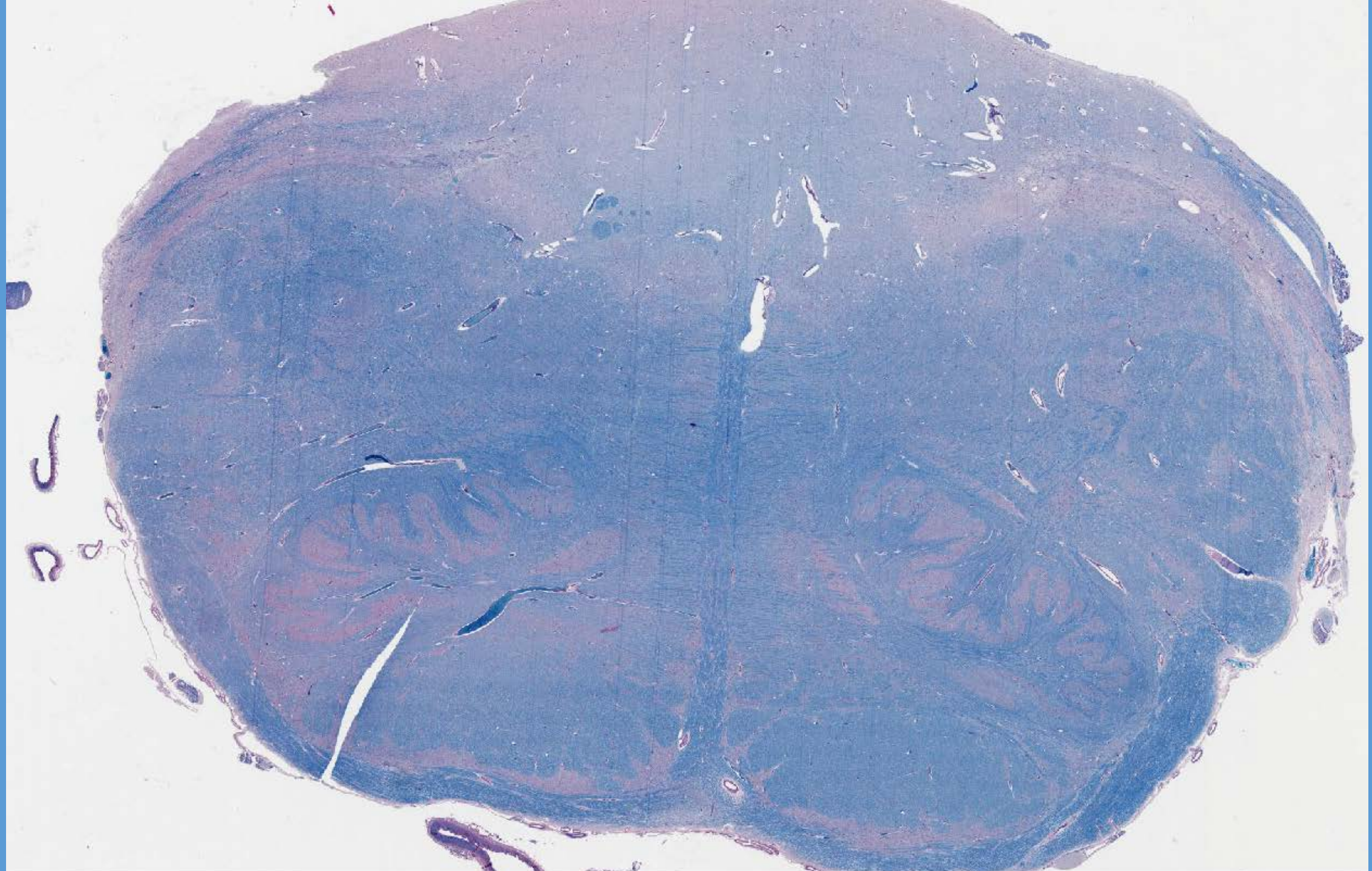


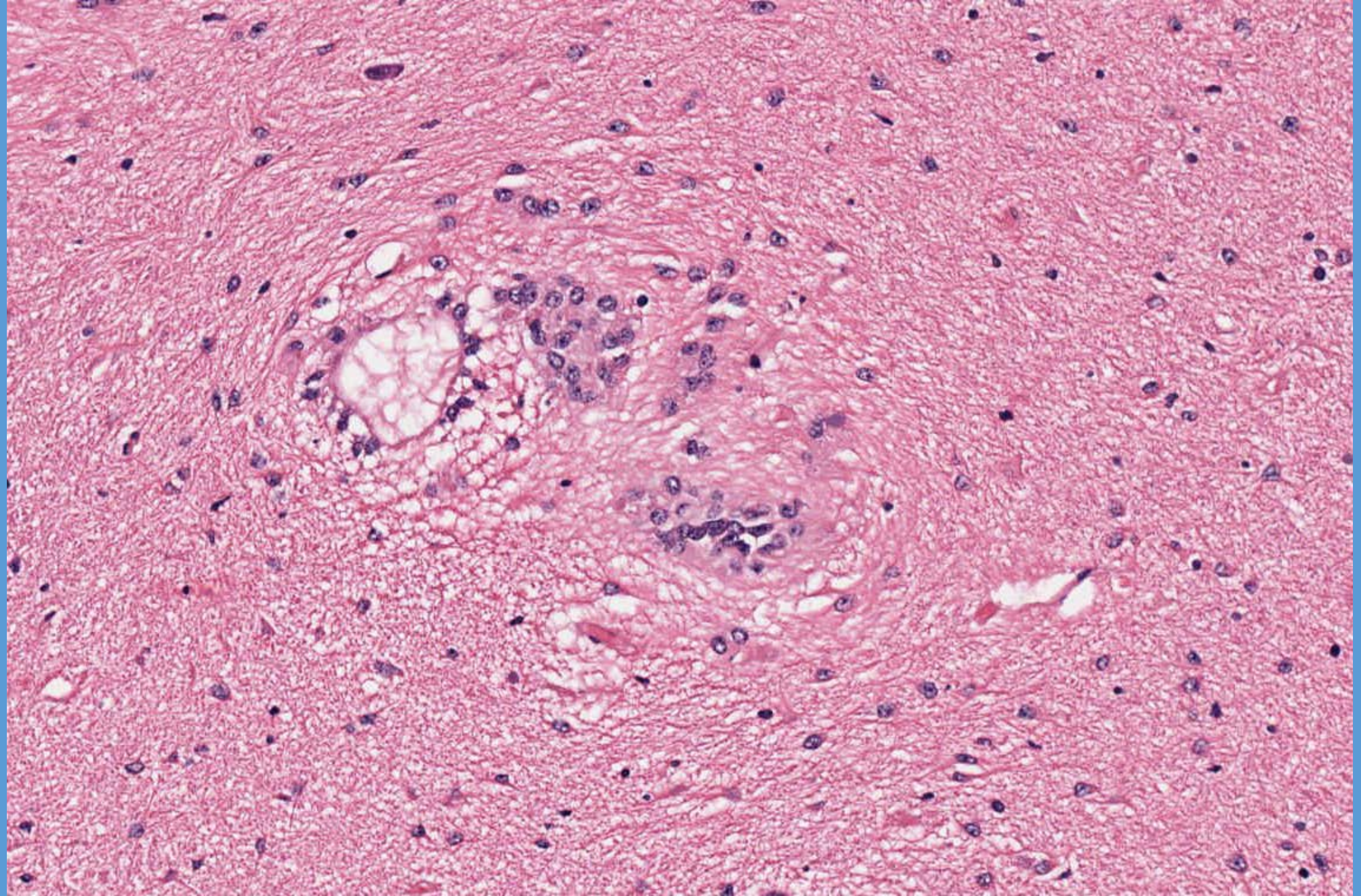
Discussion

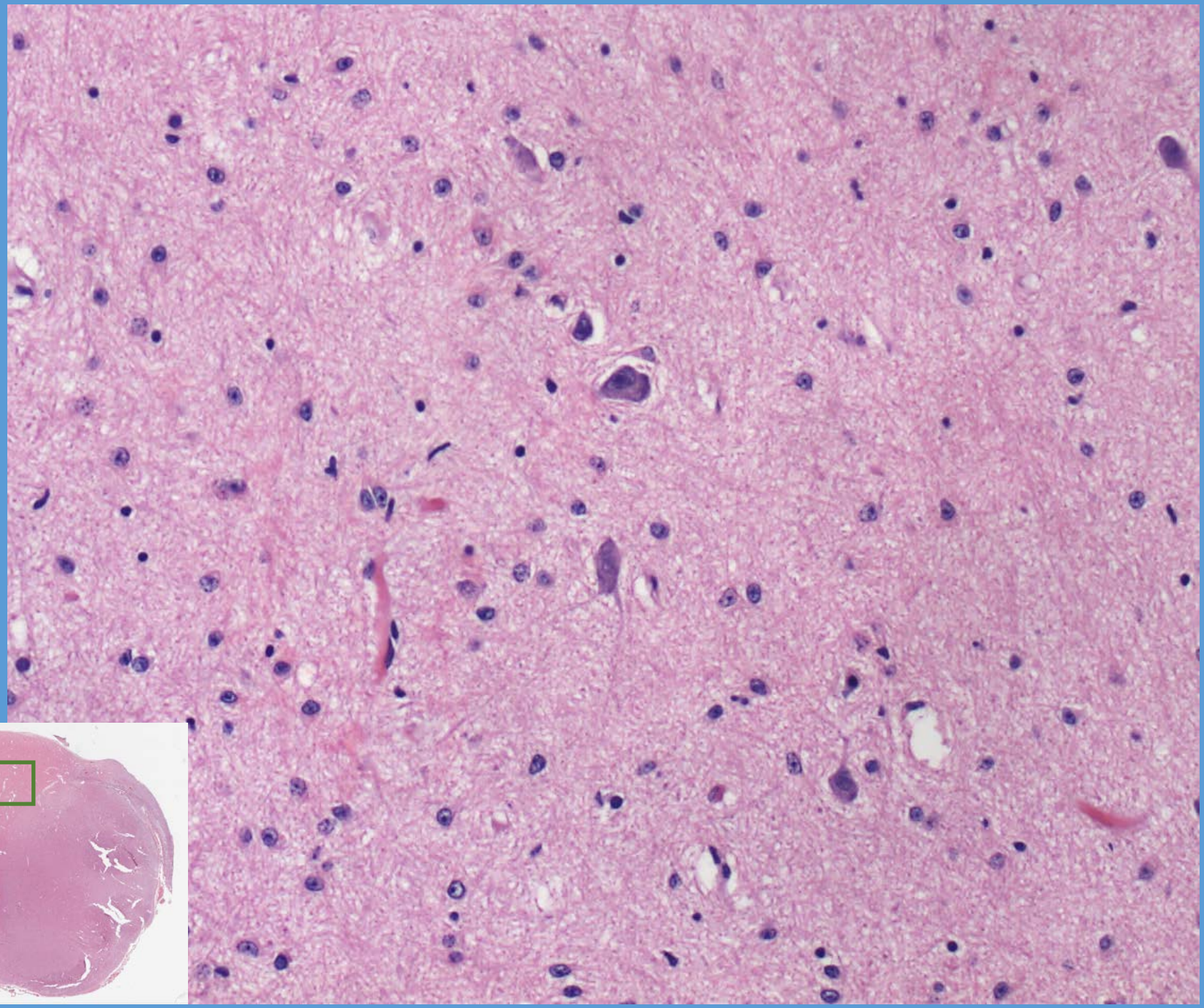
Scaled cross sections of medulla

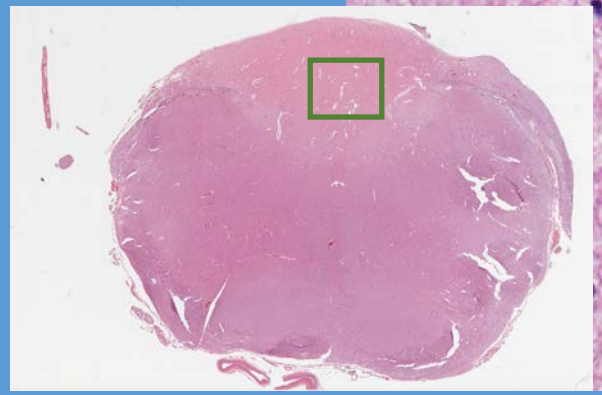


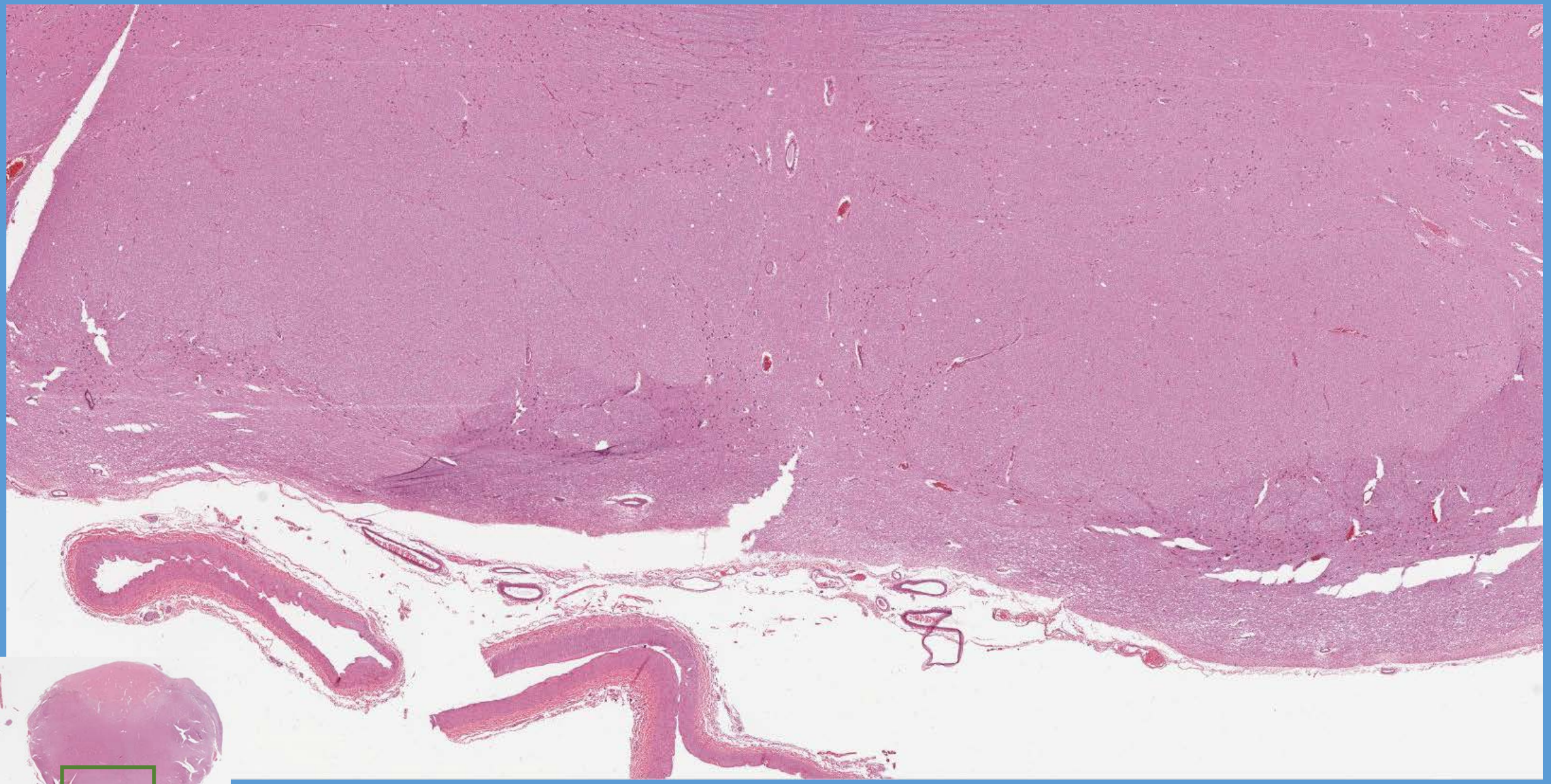




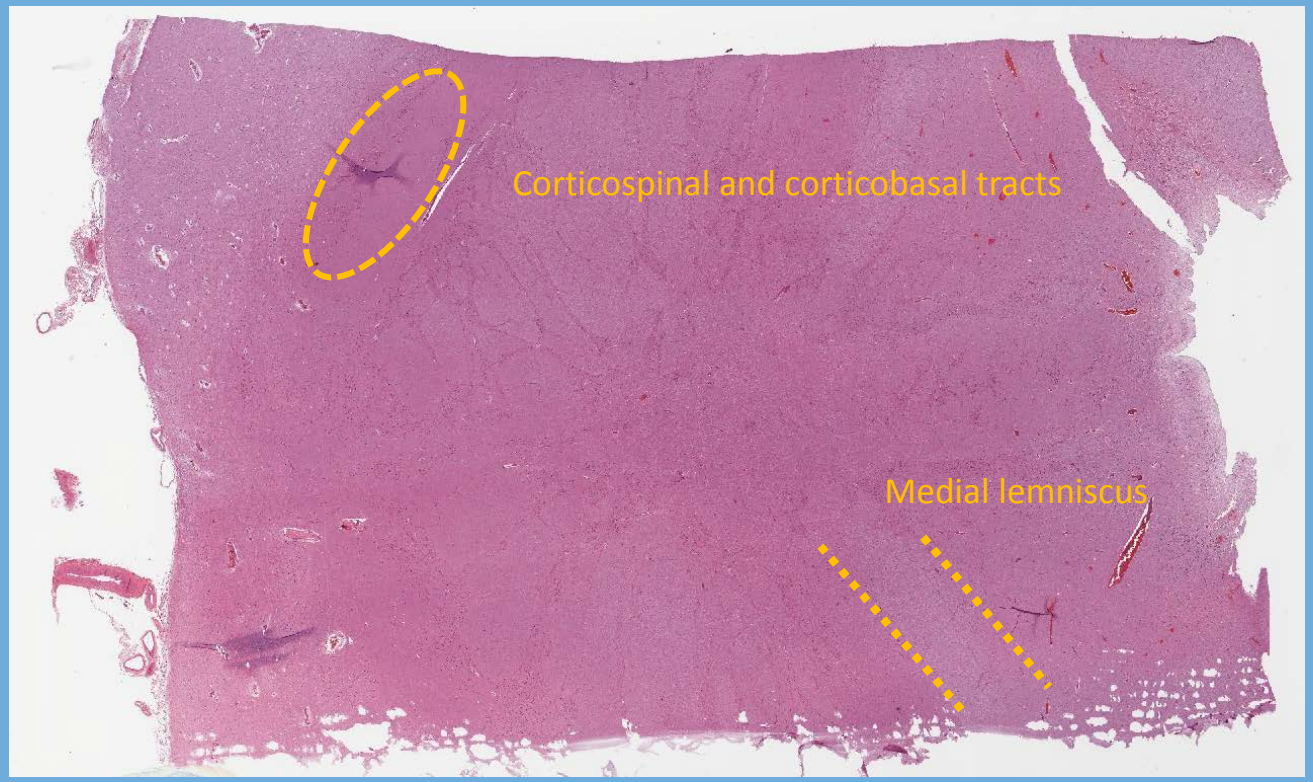


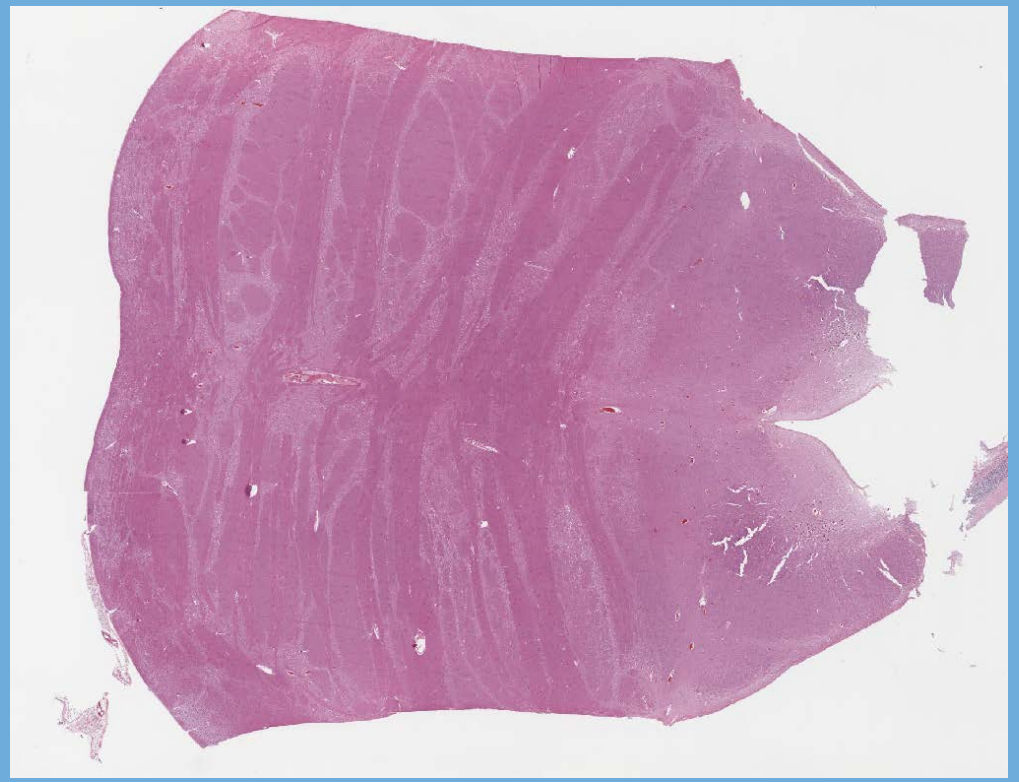


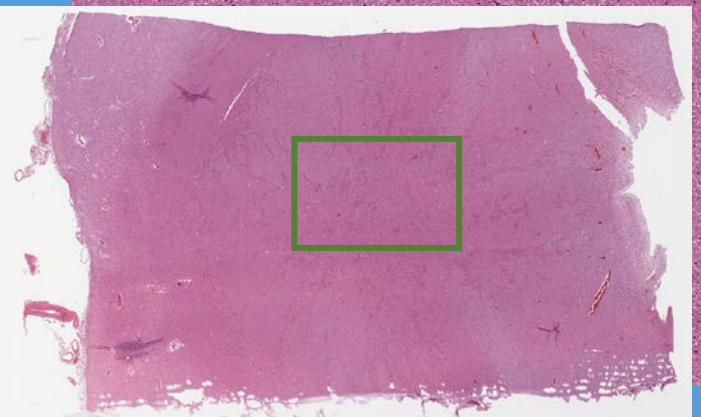


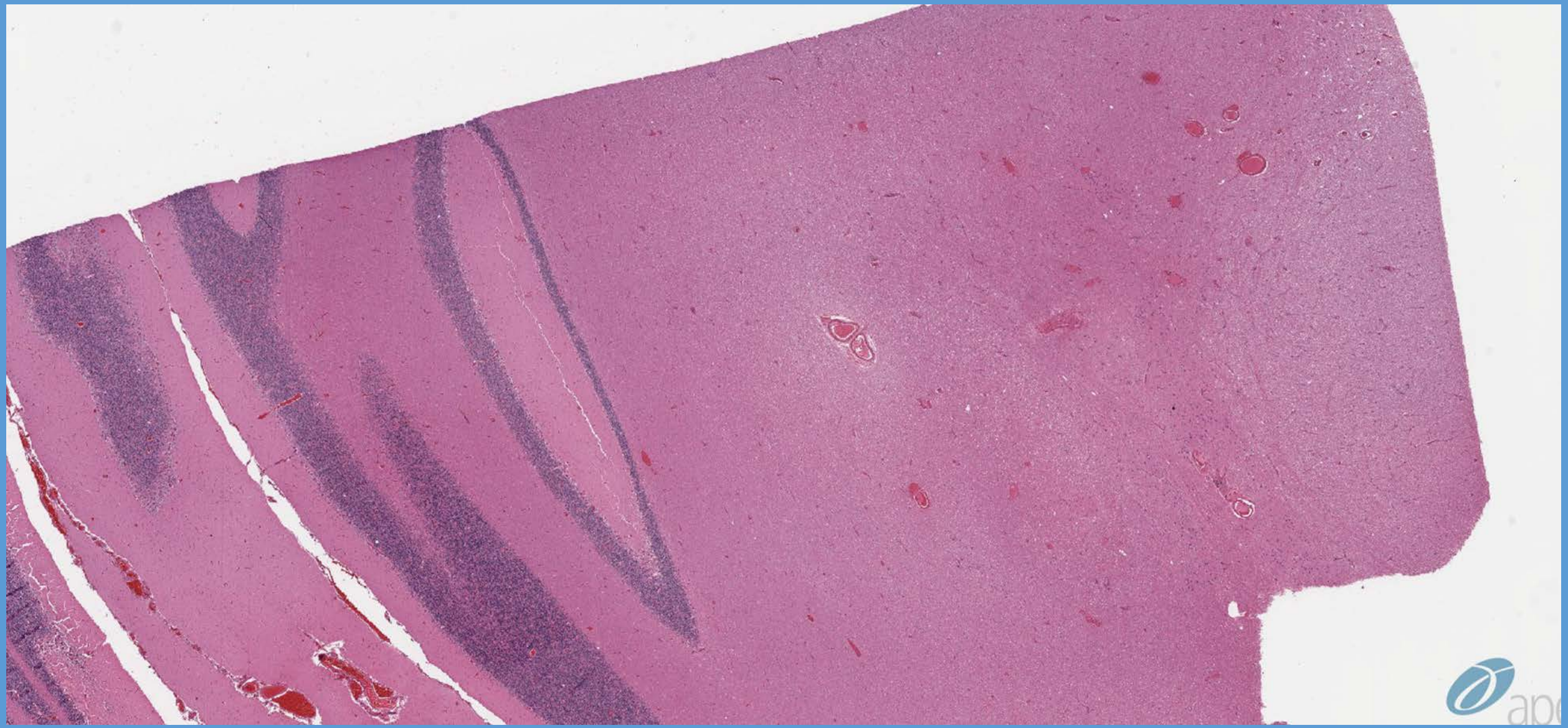


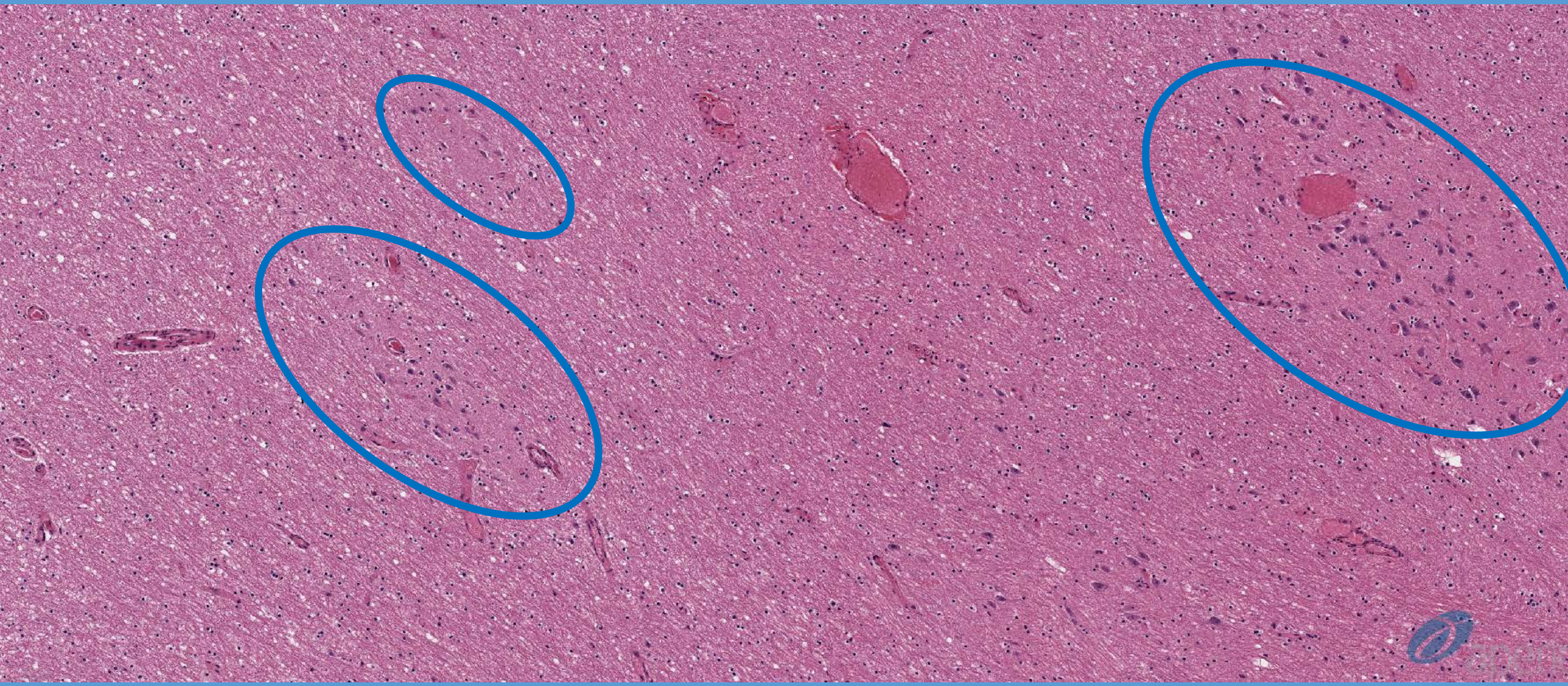
Scaled cross sections of pons











Clarification of Past Medical History……

- Fibrodysplasia Ossificans Progressiva (FOP)
  - Progressive ossification of soft tissues
  - Leads to significant disabilities and wheelchair bound by young adulthood
    - Death often due to restrictive lung disease
  - Pts with FOP have been noted to have varied neurologic symptoms such as headaches, sensory abnormalities, and movement disorders

- ACVR-1 mutation (activin receptor type 1), also known as ALK-2
  - 95% of FOP patients have a R206H mutation

NATURE GENETICS | VOLUME 46 | NUMBER 5 | MAY 2014

ACVR1 mutations and the genomic landscape of pediatric diffuse glioma

Gelareh Zadeh & Kenneth Aldape

- ACVR-1 mutation also found in a subset of diffuse intrinsic pontine gliomas
  - Up to 27%
  - Often different point mutations than FOP

- DIPG are a member of diffuse midline glioma, harboring H3 K27M mutations
  - ACVR1 and K27M appear to be mutual

Neoplastic or Hamartomatous?

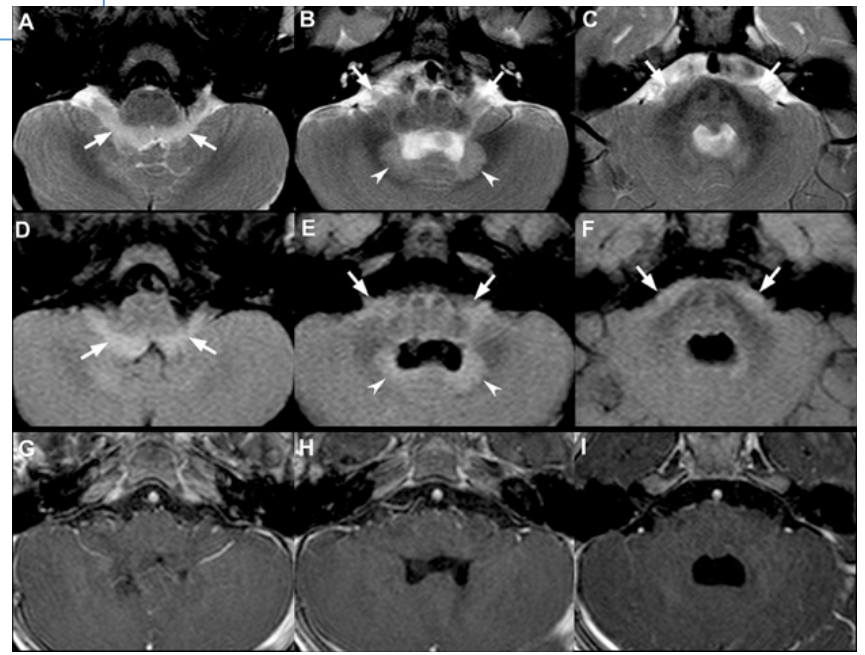
- Given the common genetic mutation as DIPG, is the brainstem mass identified in FOP patients neoplastic?

Journal of
Medical Genetics

Phenotypes
Short report

Novel asymptomatic CNS findings in patients with *ACVR1/ALK2* mutations causing fibrodysplasia ossificans progressiva

Mariasavina Severino[1], Marta Bertamino[2], Domenico Tortora[1], Giovanni Morana[1], Sara Uccella[3], Renata Bocciardi[4, 5], Roberto Ravazzolo[4, 5], Andrea Rossi[1], Maja Di Rocco[2]



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Full Length Article

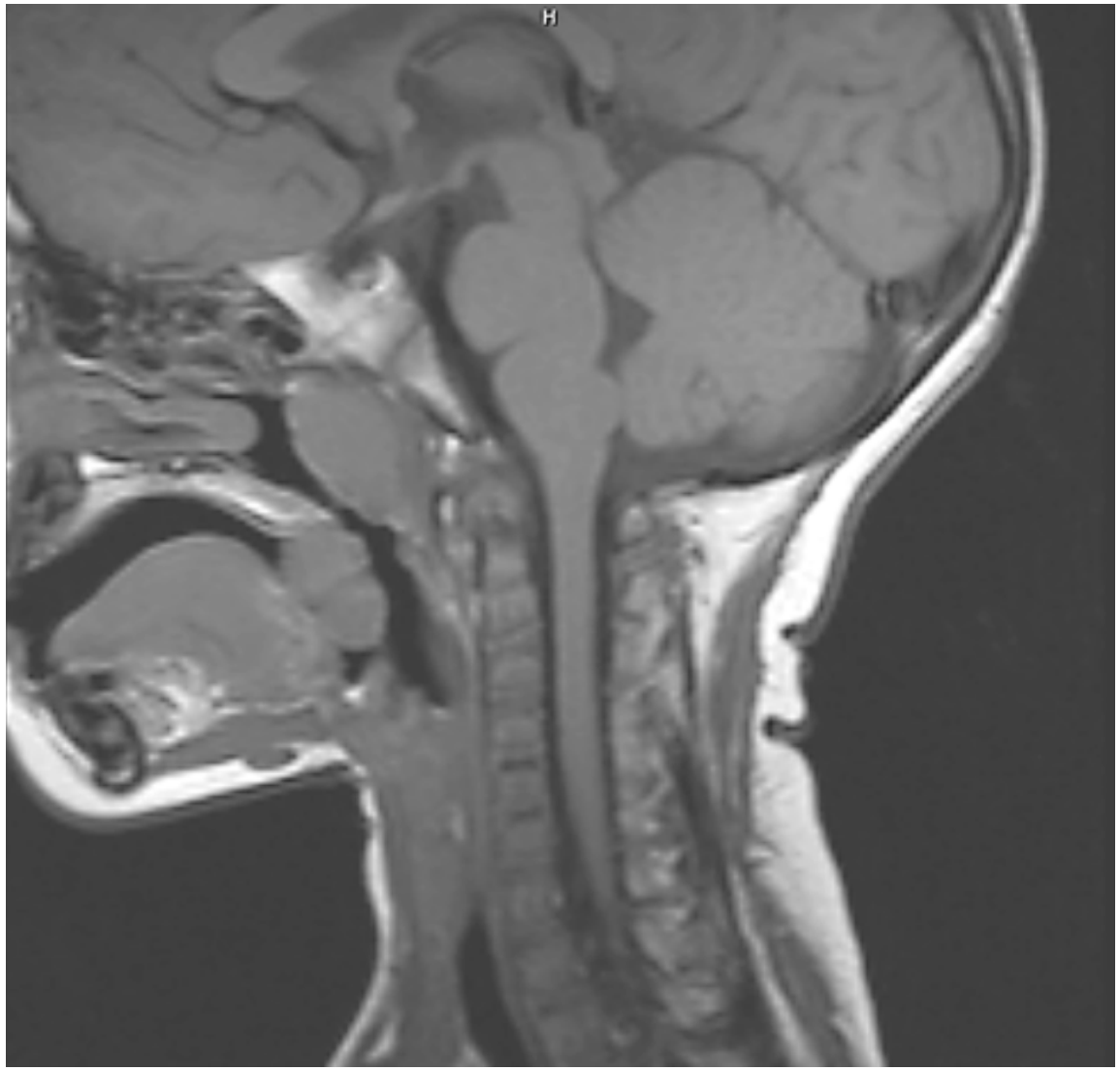
Clinical-pathological correlations in three patients with fibrodysplasia ossificans progressiva

Kelly L. Wentworth [a,*], Katherine Bigay [a,1], Tea V. Chan [a,1], Jennifer P. Ho [a,1], Blanca M. Morales [a], Joseph Connor [c], Erin Brooks [c], M. Shahriar Salamat [c], Henry Charles Sanchez [b], Geoffrey Wool [f], Robert J. Pignolo [d], Frederick S. Kaplan [e], Edward C. Hsiao [a,*]

Imaging Insights

- High T2 & ADC values indicate low cellularity, absence of contrast, & longterm stability are consistent with hamartomas

- CNS involvment in asymptomatic children included T2 dentate nuclei abnormalities, & signal abnormalities of the dorsal pons



- *Severino M, Bertamino M, Tortora D, et al Novel asymptomatic CNS findings in patients with ACVR1/ALK2 mutations causing fibrodysplasia ossificans progressivaJournal of Medical Genetics 2016;53:859-864.*

Summary

- Diagnosis: Glioneuronal hamartomatous proliferation of the brainstem in a patient with fibrodysplasia ossificans progressiva
- Our pathology supports radiographic interpretation of hamartoma
- ACVR1 mutations found in DIPG and FOP
  - Differing point mutations
  - Suggests that ACVR1 is probably not the driving mutation in DIPG
- Potential for misdiagnoses as DIPG

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5. Severino M, et al. Novel asymptomatic CNS findings in patients with ACVR1/ALK2 mutations causing fibrodysplasia ossificans progressiva. J Med Genet. 2016 Dec;53(12):859-864.
6. Wentworth KL et al. Clinical-pathological correlations in three patients with fibrodysplasia ossificans progressiva. Bone. 2018 Apr;109:104-110