28th Annual Course in Pathology - Pittsburgh

Neuro-Oncologic DM

Case Studies

Gregory N. Fuller, MD, PhD

Professor of Pathology and Neuroradiology

Deputy Chair, Anatomical Pathology

Chief Neuropathologist

The University of Texas MD Anderson Cancer Center

CASE STUDIES

The University of Texas M D Anderson Cancer Center

Integrative Diagnostic Medicine Case Conference

IDMCC

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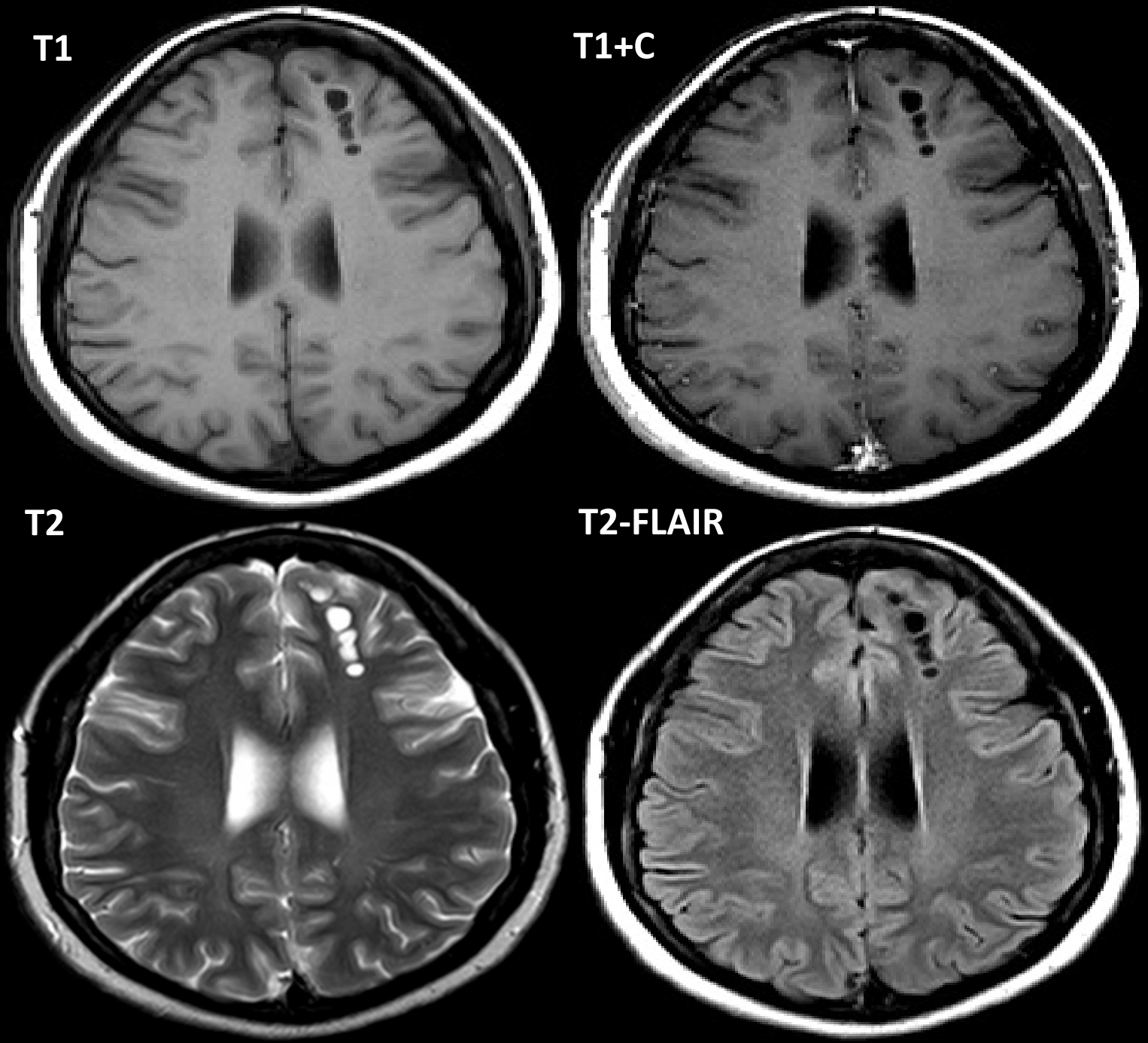
Chief Neuropathologist

Patient 1

A 30-something-year-old woman presented with complaint of headache.

MR imaging studies showed a non-enhancing, multicystic left frontal lobe lesion.


T1
T1+C
T2
T2-FLAIR

Brief History

- Patient underwent **Subtotal Resection** at a local hospital

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- Residual tumor treated with **Stereotactic Radiosurgery (SRS)**
- Surveillance imaging showed **NO EFFECT of SRS on residual tumor**

Brief History

Patient self-referred to MDACC for a second opinion on treatment options.

Brief History

As part of **standard MDACC procedure**, the **biopsy slides**, **all** **reference lab reports**, and the **preoperative MR imaging studies**

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by the PATHOLOGIST!

Brief History

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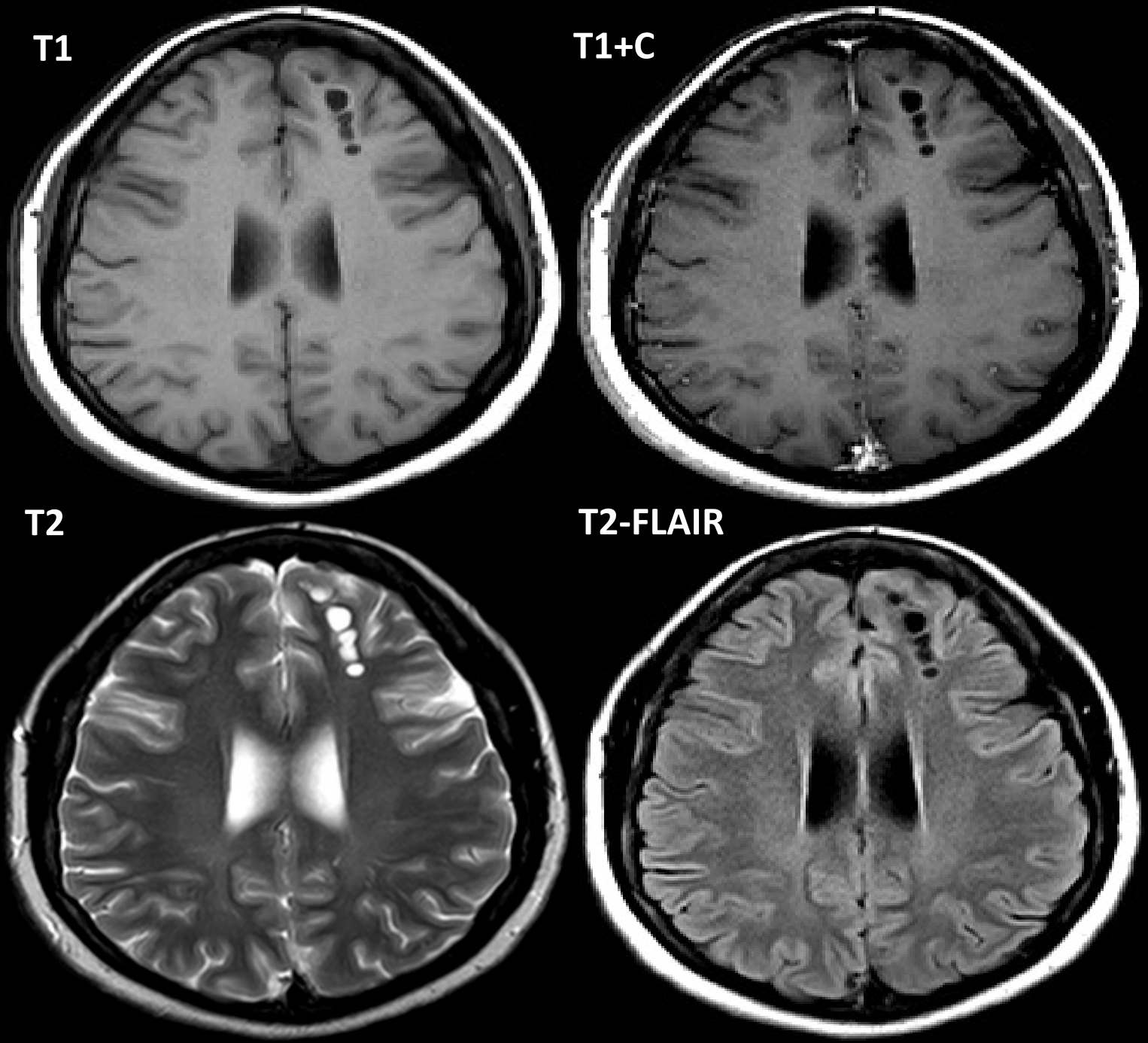
T1
T1+C
T2
T2-FLAIR

What was the MDACC Dx?

MILDY HYPERCELLULAR WHITE MATTER

Here’s the thing...

Diagnostic Medicine physicians don't actually *do* anything...

Diagnostic Medicine physicians don't actually *do* anything...

But we know stuff.

Stuff that saves patient lives every day.

DIAGNOSIS

(redacted)

special studies were performed at MDACC

(IDH1-R132H, ATRX, p53 protein), brain, left frontal lobe, open biopsy:

Mildly hypercellular white matter.

"The imaging features of the lesion bear resemblance to those seen in the entity Tumefactive Dilated Perivascular Spaces"

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References
1. Rohlfs J, et al. Enlarged perivascular spaces mimicking multicystic brain tumors. J Neurosurg 102:1142–1146, 2005.
2. Ogawa T, et al. Unusual widening of Virchow-Robin spaces: MR Appearance. Am J Neuroradiol 16:1238–1242, 1995.
3. Salzman KL, et al. Giant tumefactive perivascular spaces. Am J Neuroradiol 26:298–305, 2005.
4. Stephens T, et al. Giant tumefactive perivascular spaces. J Neurological Sci 266;171-173, 2008.

"The imaging features of the lesion bear resemblance to those seen in the entity Tumefactive Dilated Perivascular Spaces"

Rohlfs *J Neurosurg 2005* PMID 16028777

J Neurosurg 102:1142–1146, 2005

Enlarged perivascular spaces mimicking multicystic brain tumors

Report of two cases and review of the literature

JOCHEN ROHLFS, M.D., THOMAS RIEGEL, M.D., MUNZIR KHALIL, M.D., JOANNA IWINSKA-ZELDER, M.D., HANS-DIETER MENNEL, M.D., PH.D., HELMUT BERTALANFFY, M.D., PH.D., AND DIETER HELLWIG, M.D., PH.D.

Departments of Neurosurgery, Neuroradiology, and Neuropathology, Philipps University, Marburg, Germany

Stephens *J Neurol Sci 2008* PMID 17888454

Journal of the Neurological Sciences

Journal of the Neurological Sciences 266 (2008) 171–173

www.elsevier.com/locate/jns

Short communication

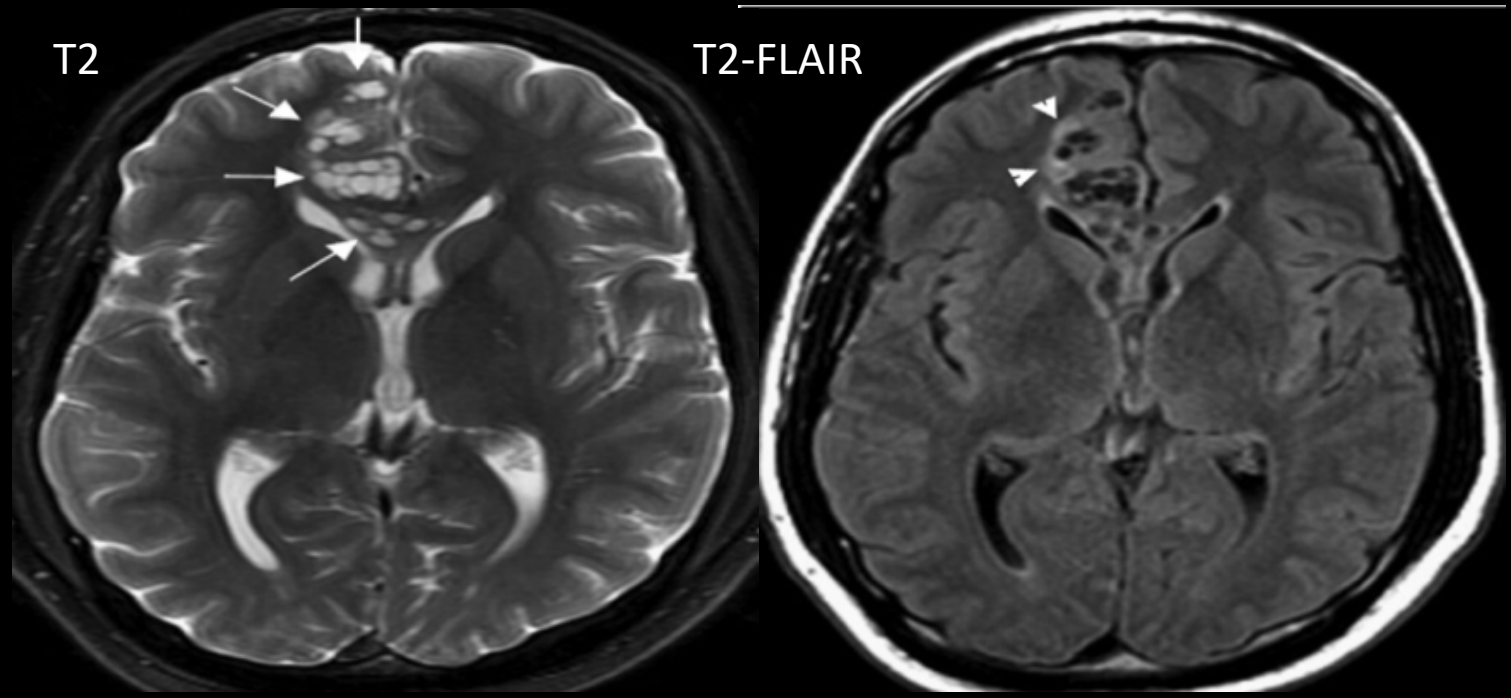
Giant tumefactive perivascular spaces

Tausha Stephens [a], Hemant Parmar [a,*], Wayne Cornblath [b]

[a] *Department of Radiology, University of Michigan Health System, Ann Arbor, Michigan, USA*
[b] *Department of Neuro-Opthalmology, University of Michigan Health System, Ann Arbor, Michigan, USA*

Received 26 June 2007; received in revised form 20 August 2007; accepted 22 August 2007
Available online 20 September 2007

Stephens et al
PMID: 17888454



Stephens et al
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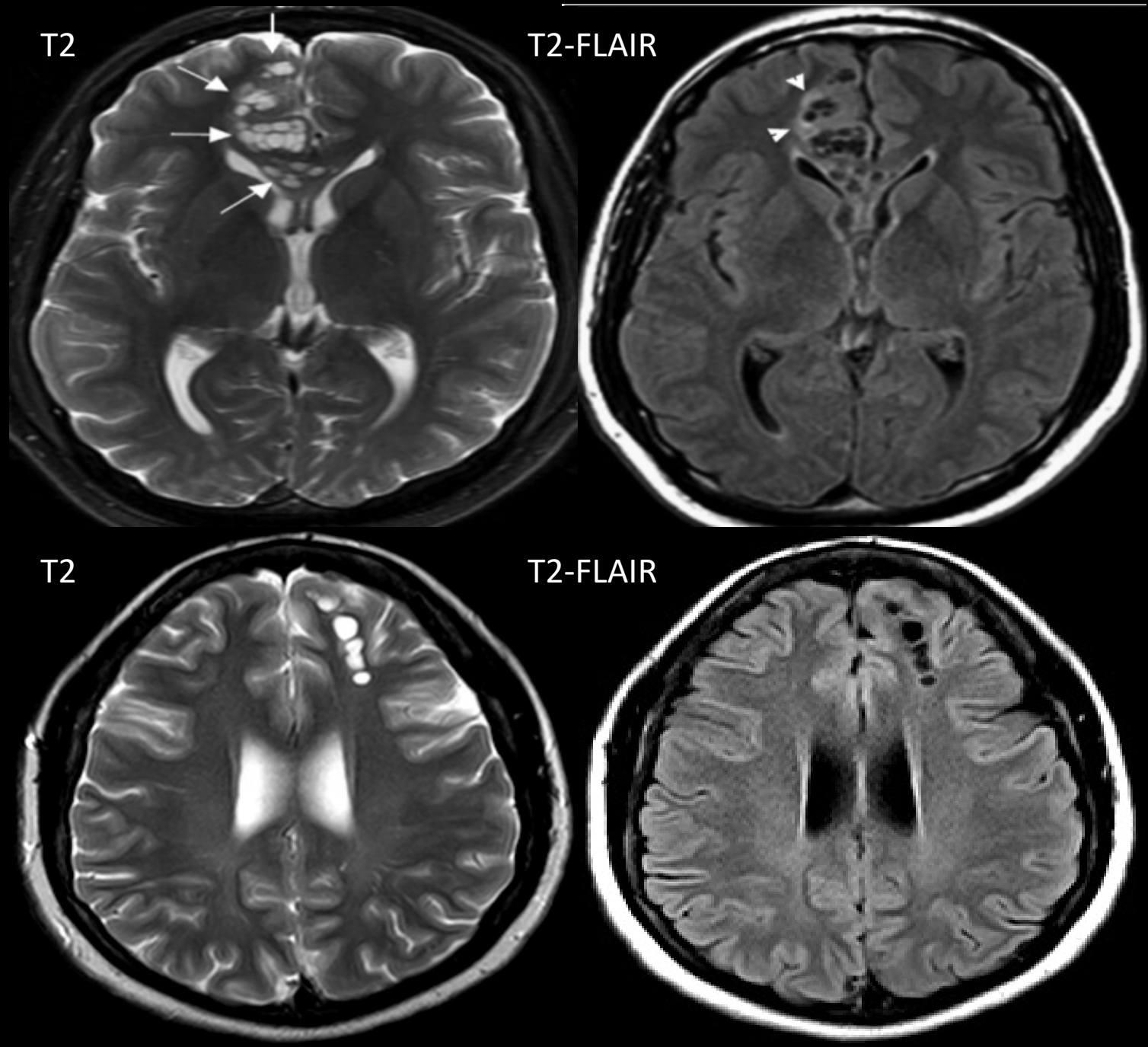
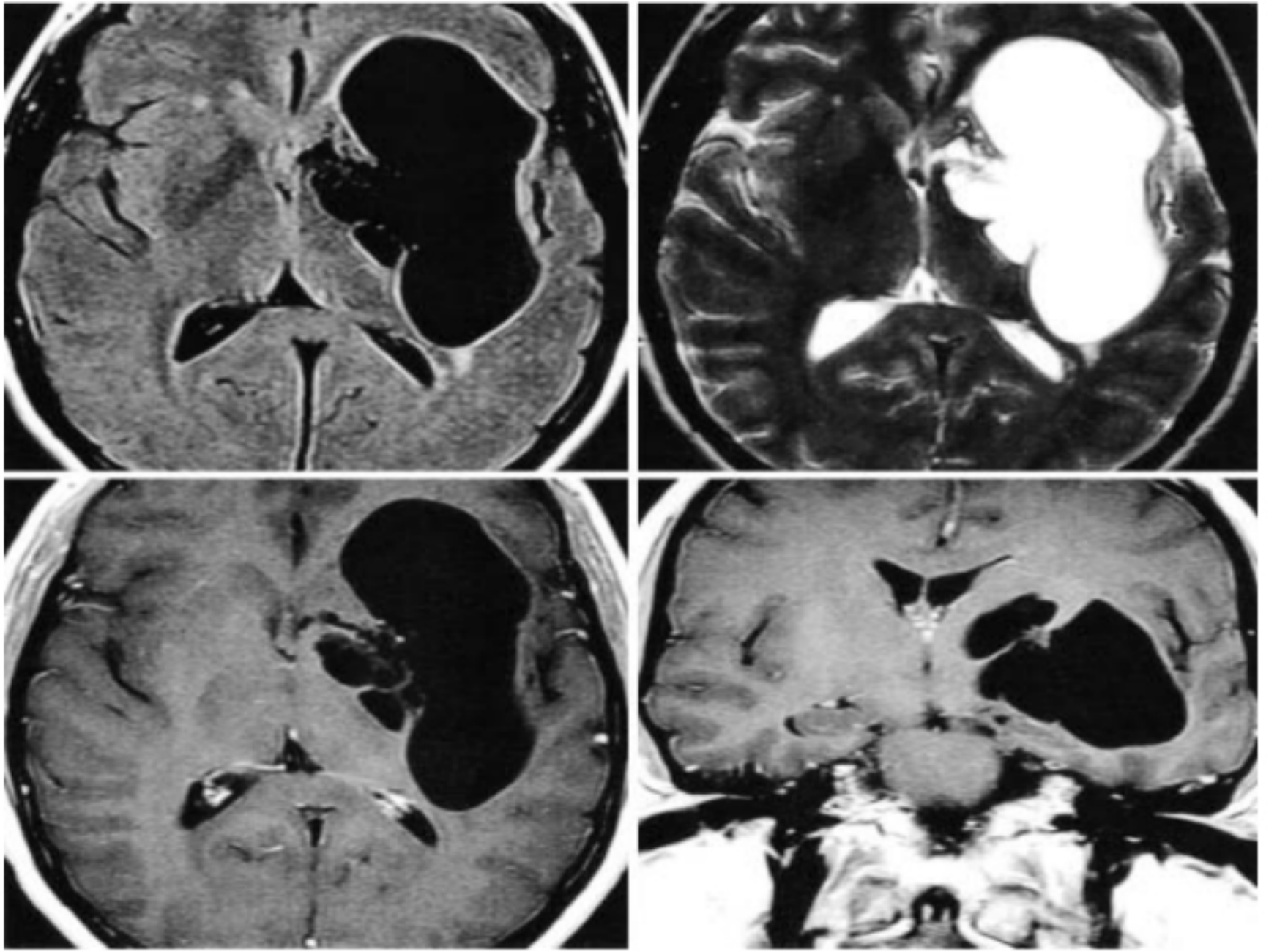


MDACC



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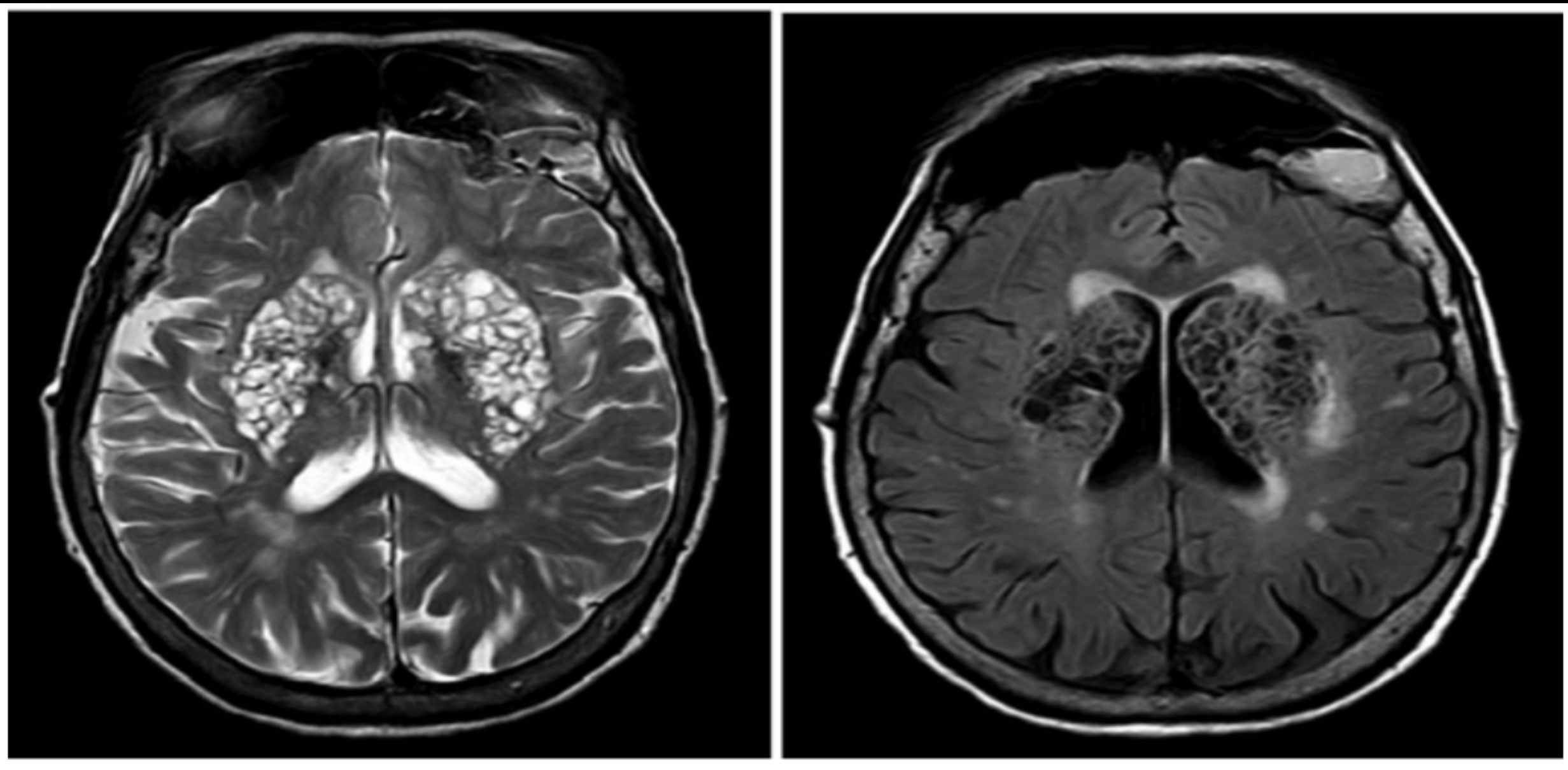
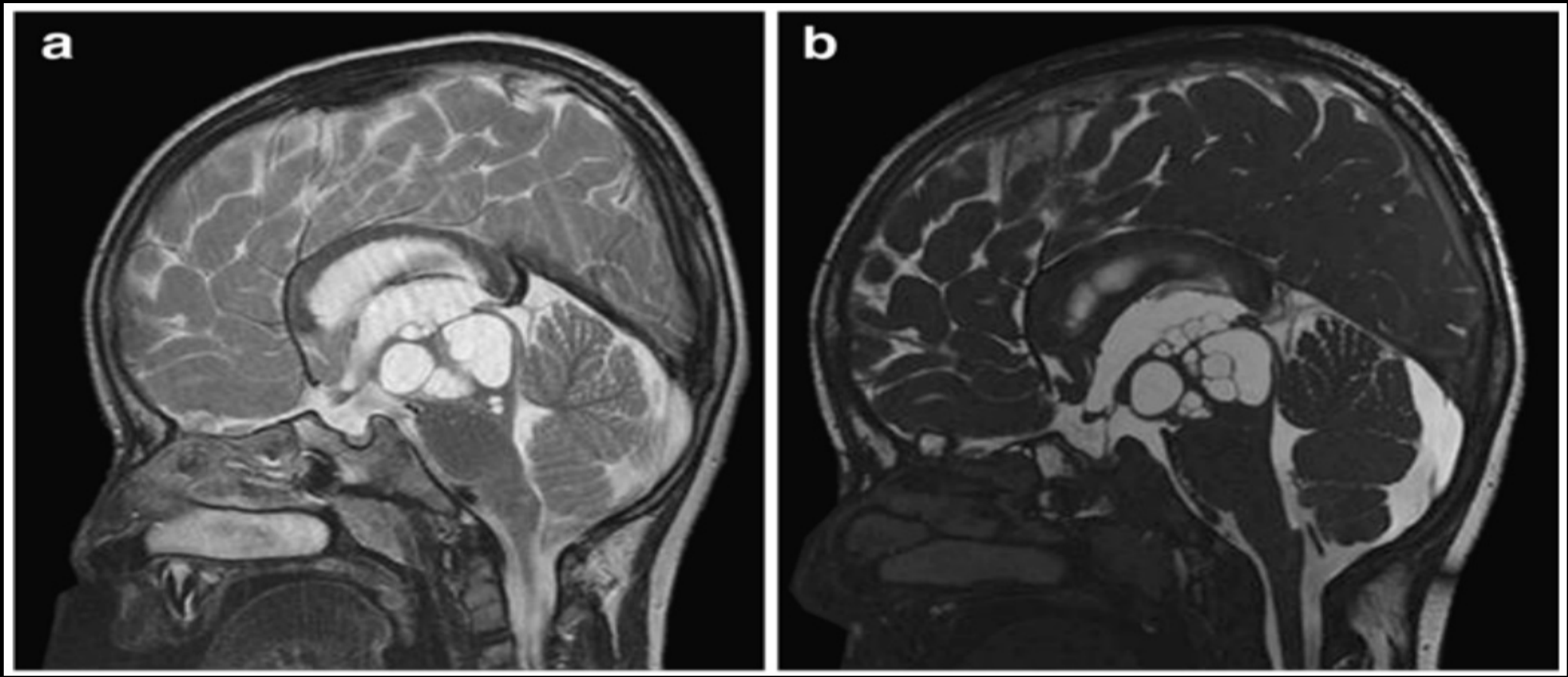
PMID 15137600



Zacharia T *J Neuroimaging* 2011
PMID 19888927



Fayeye O et al. *Child's Nerv Sys* 2010
PMID 20437240

Tumefactive Perivascular Space Alteration

exhibits a

spectrum of morphology

Tumefactive Perivascular Space Alteration

exhibits a

spectrum of morphology

just like tumors do!

Why was this diagnosis so easy to make?

NOT because of the distinctive histologic features

NOT because of the distinctive histologic features

NOT because of a distinctive molecular signature

Because the **PATHOLOGIST,** being a

Because the **PATHOLOGIST**, being a

Physician-Pathologist

Because the **PATHOLOGIST**, being a

Physician-Pathologist

was very familiar with the

IMAGING PRESENTATION

of the entity!

Imaging *is* Pathology!

Patient 2

28-year-old male

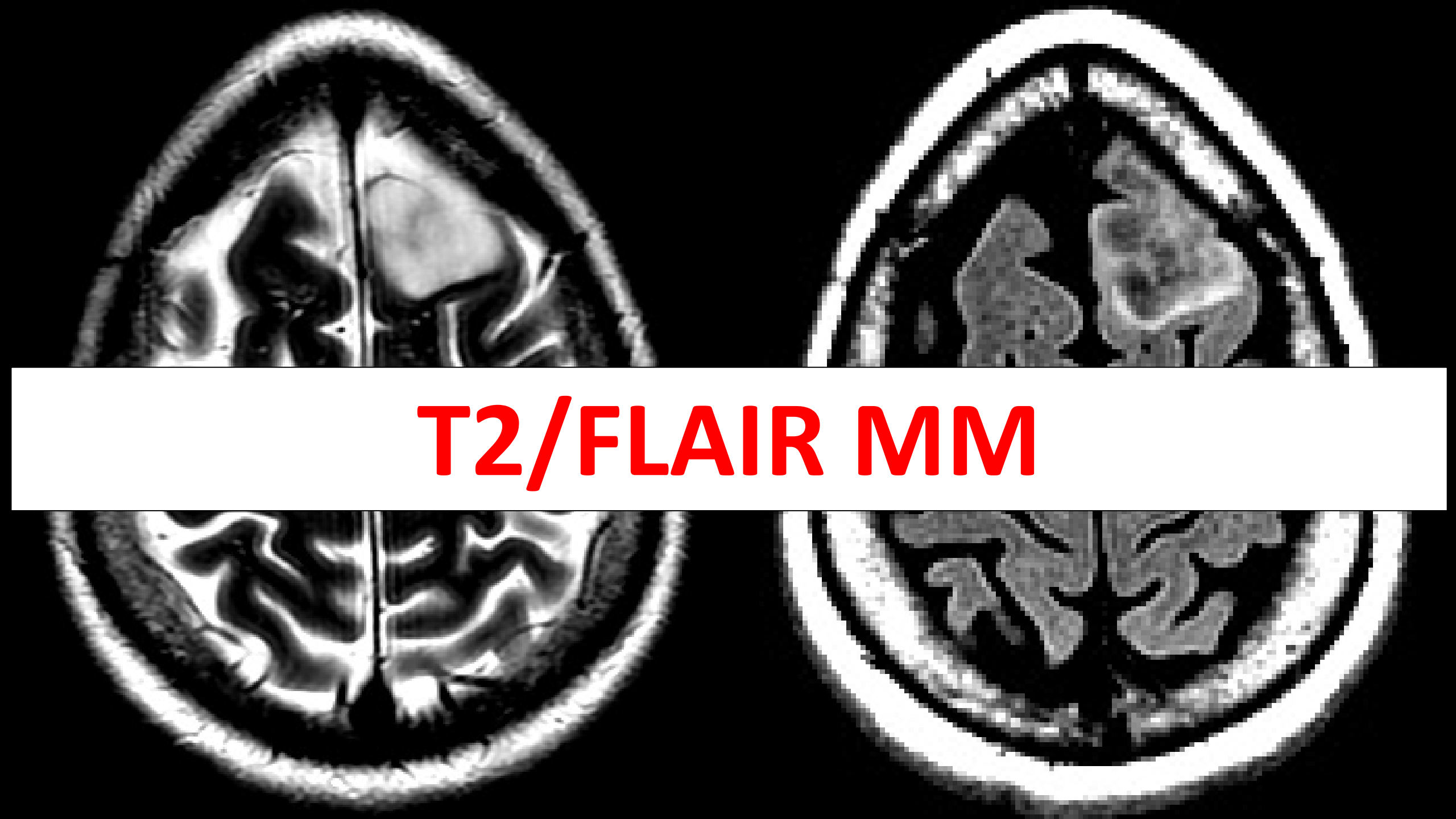
2009

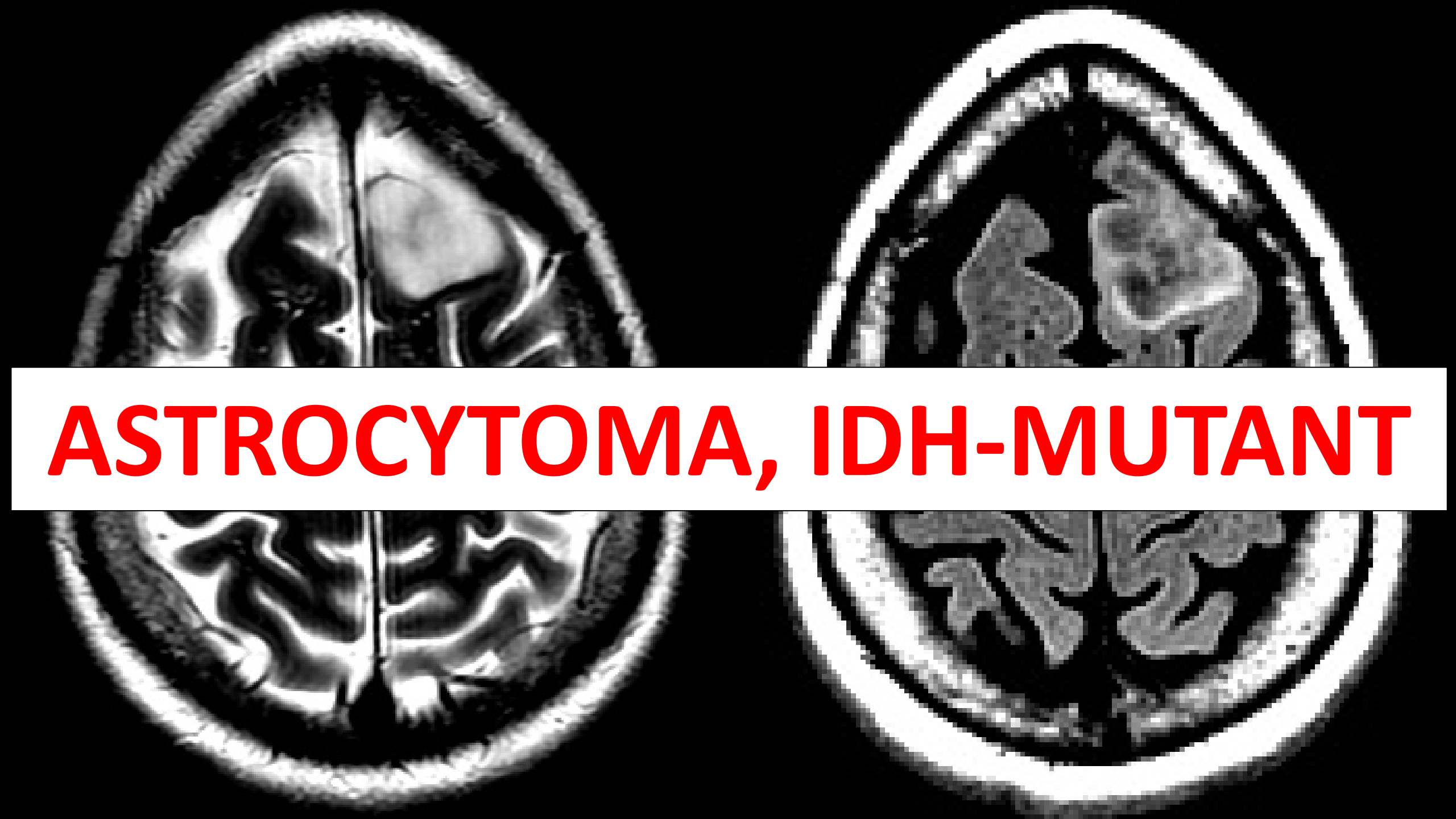
Histopathologic DX:

Mixed Oligoastrocytoma

What does the next slide show?


DX?


T2/FLAIR MM



ASTROCYTOMA, IDH-MUTANT

DNA Methylation Profiling

NOT REQUIRED

600-Gene NGS

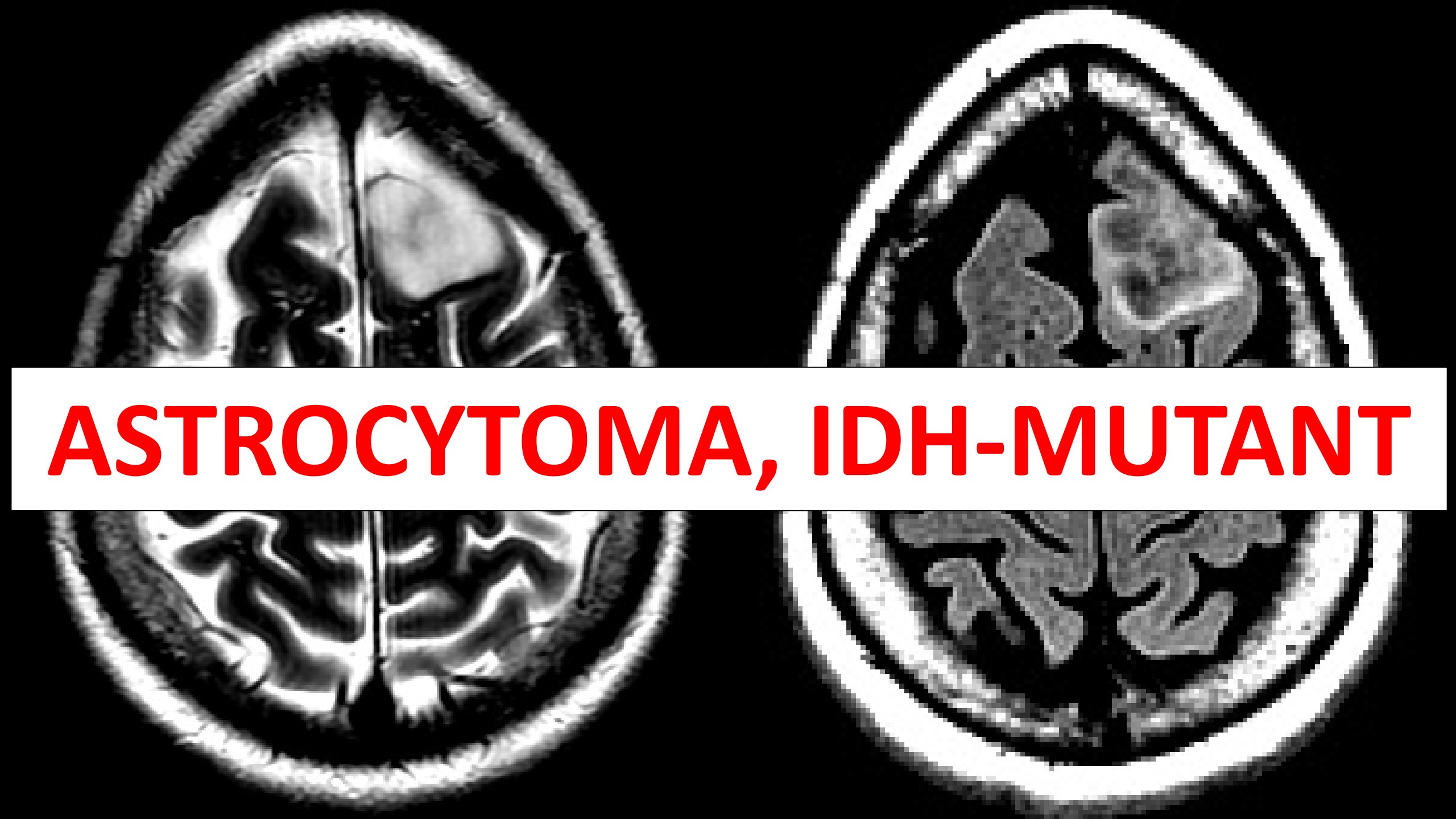
NOT REQUIRED

Surrogate Immunophenotyping

NOT REQUIRED

BIOPSY

NOT REQUIRED



ASTROCYTOMA, IDH-MUTANT

Would we treat this patient without a tissue-confirmed diagnosis?

No.

Biopsy is required.

For several reasons.

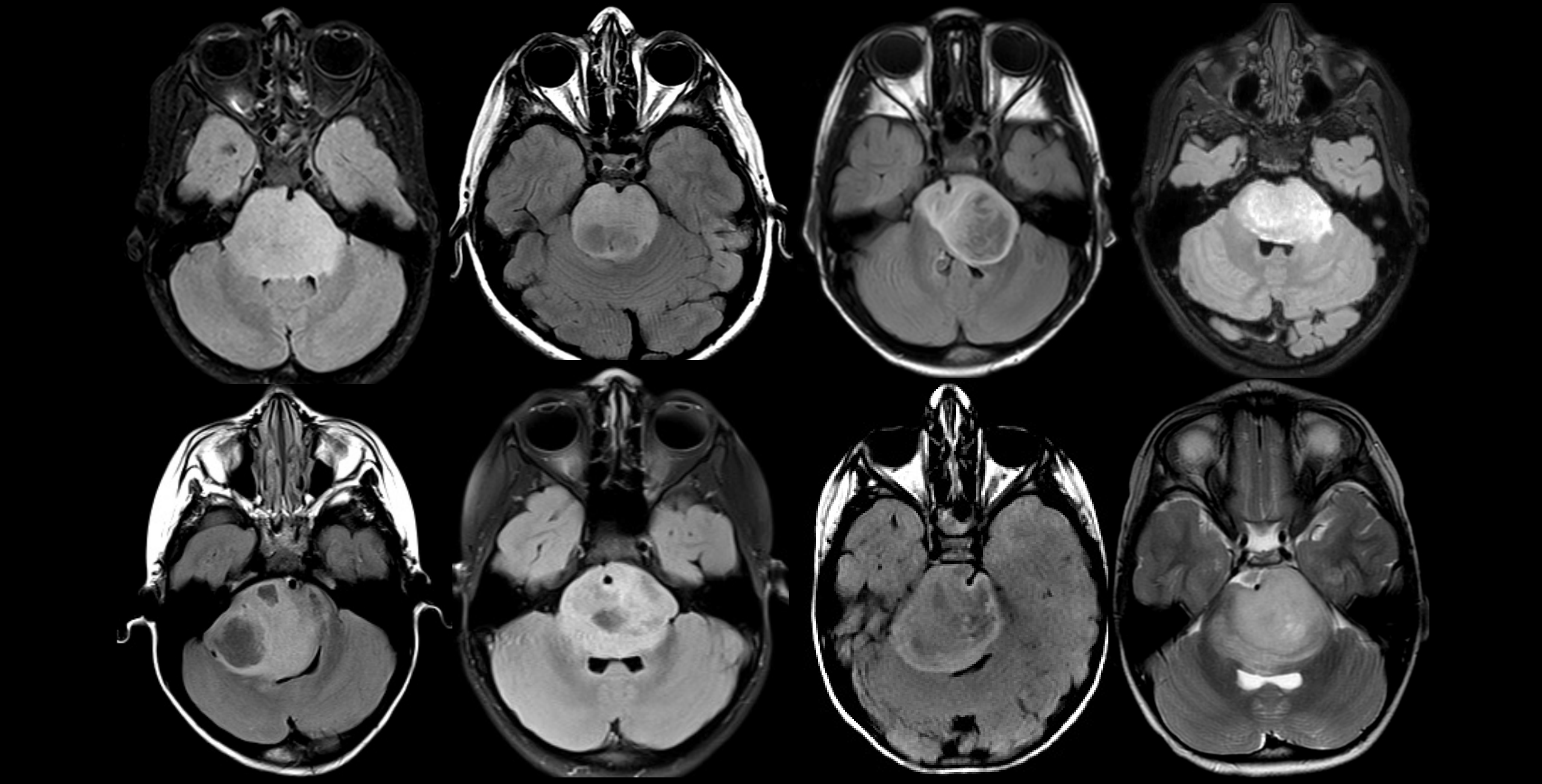
Preop imaging does NOT give the *CDKN2A/B* status, or data for other clinically-relevant markers/targets

Underserved country application?

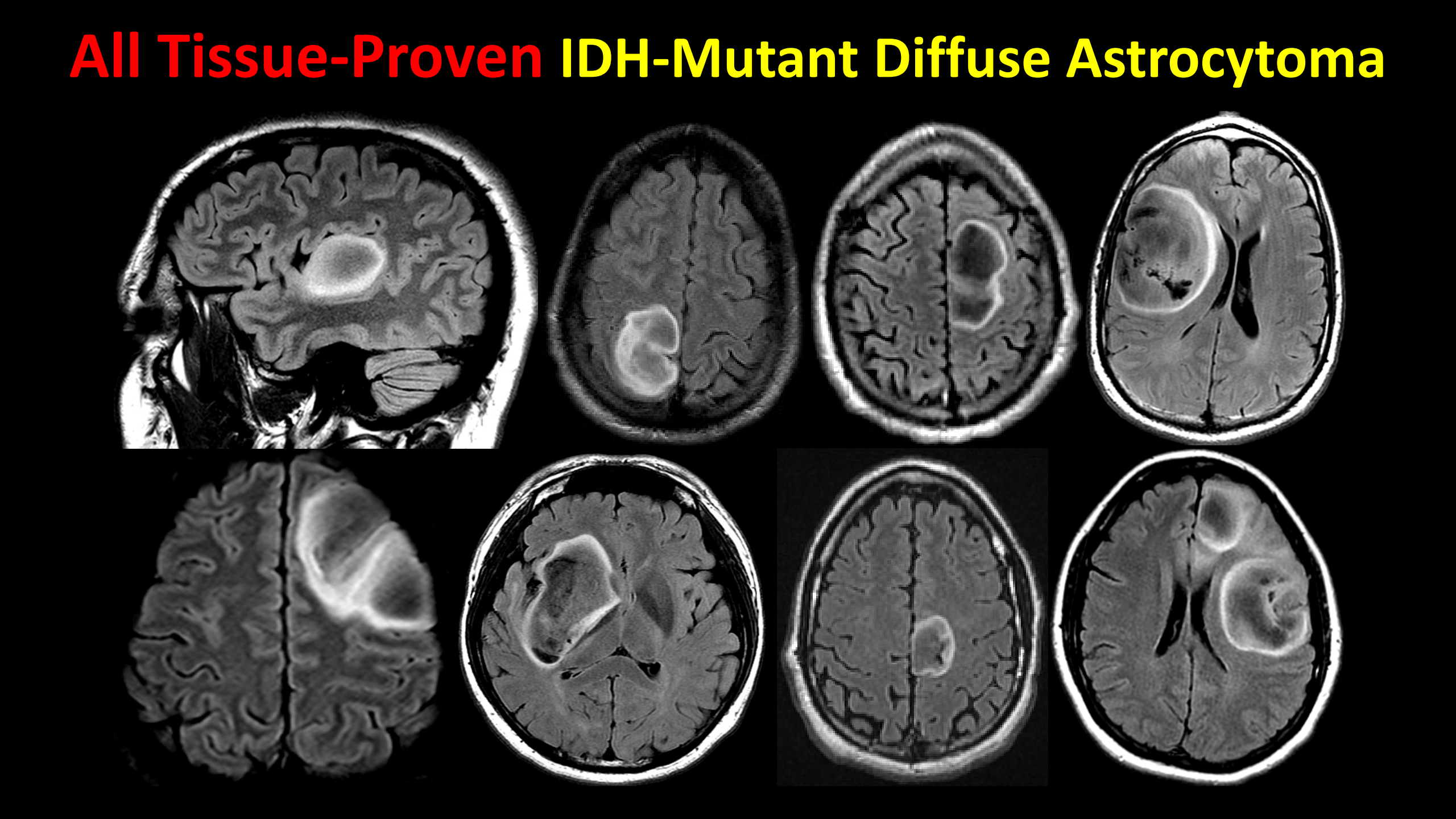
Might there be countries that have MR Imaging, but no access to PCR/NGS/DNA Meth Profiling?

Is there any precedence in countries that *do* have all of these advanced technologies to treat a newly-identified primary brain mass based solely on imaging, without biopsy?

Diffuse Intrinsic Pontine Glioma (DIPG) Spectrum of Imaging Morphology (8 Patients)



All Tissue-Proven IDH-Mutant Diffuse Astrocytoma



The presence of classical unequivocal T2/FLAIR Mismatch in an adult patient with a diffuse glioma has a positive predictive value for IDH-Mutant Diffuse Astrocytic Disease approaching 100%

The presence of classical unequivocal T2/FLAIR Mismatch in an adult patient with a diffuse glioma has a positive predictive value for IDH-Mutant Diffuse Astrocytic Disease approaching 100%

By comparison, the positive predictive value of preop imaging for DMG, H3 K27-Altered is only about 85%

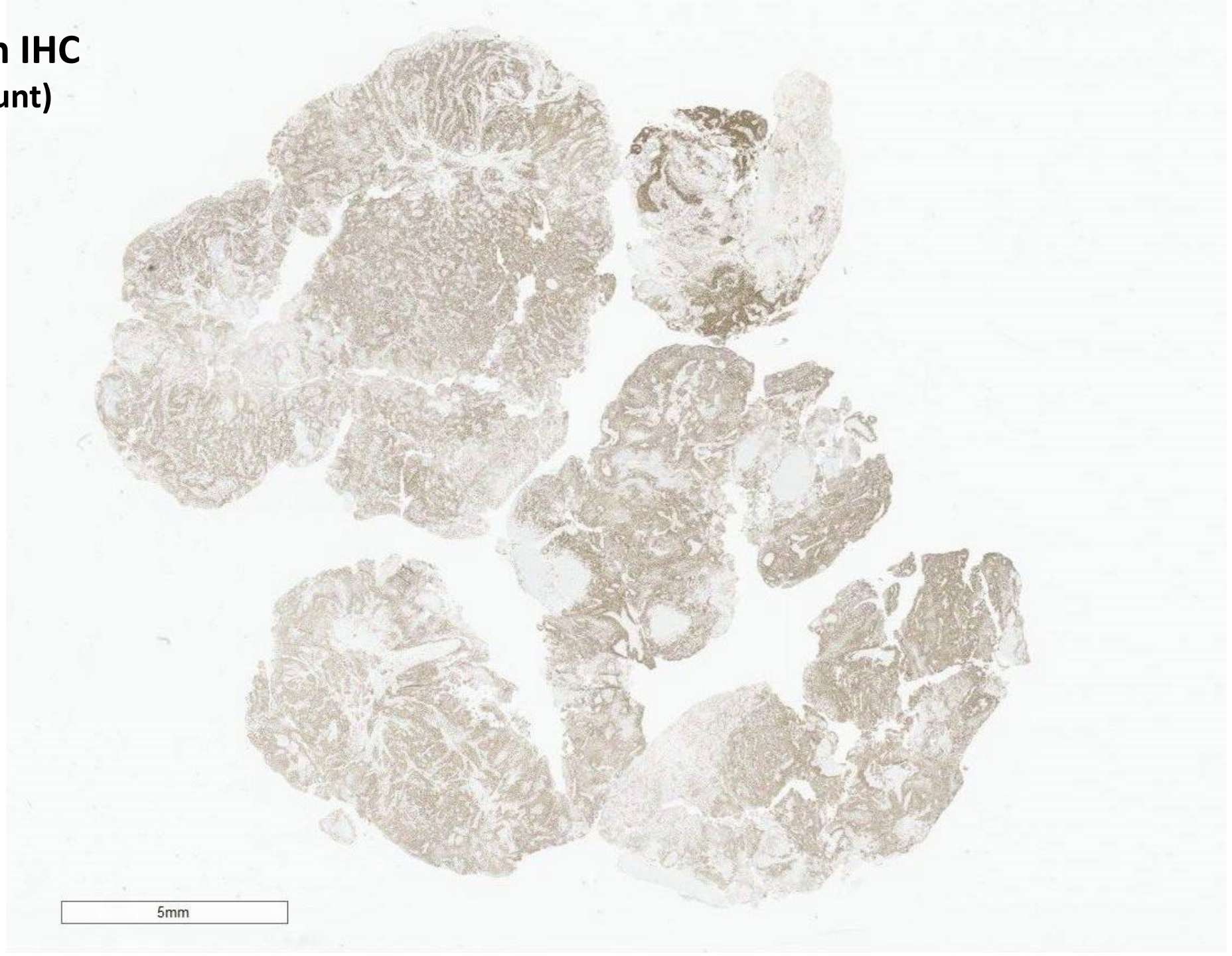
Patient 3

57-year-old male

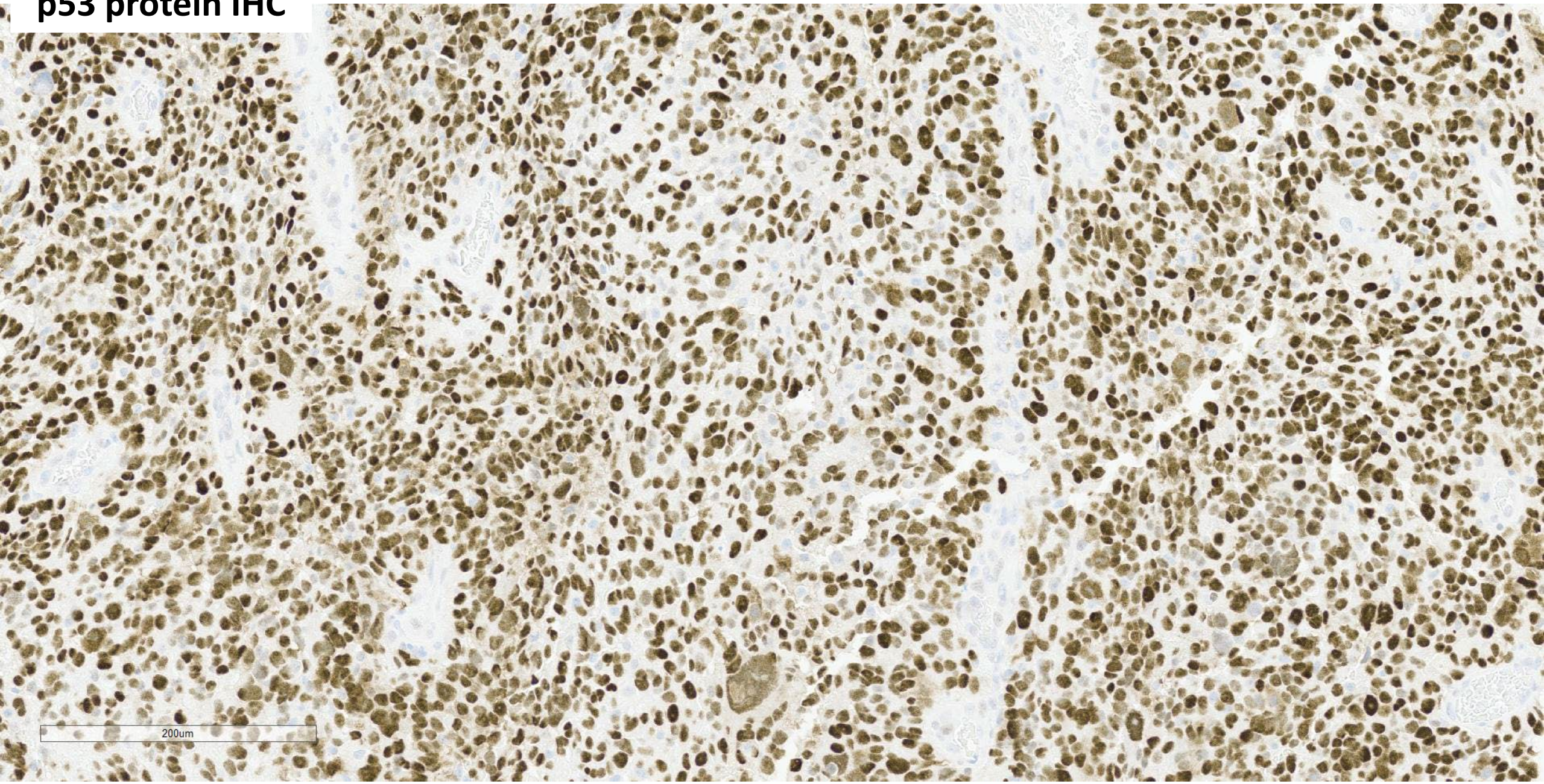
Molecular Signature

Surrogate Immunophenotyping

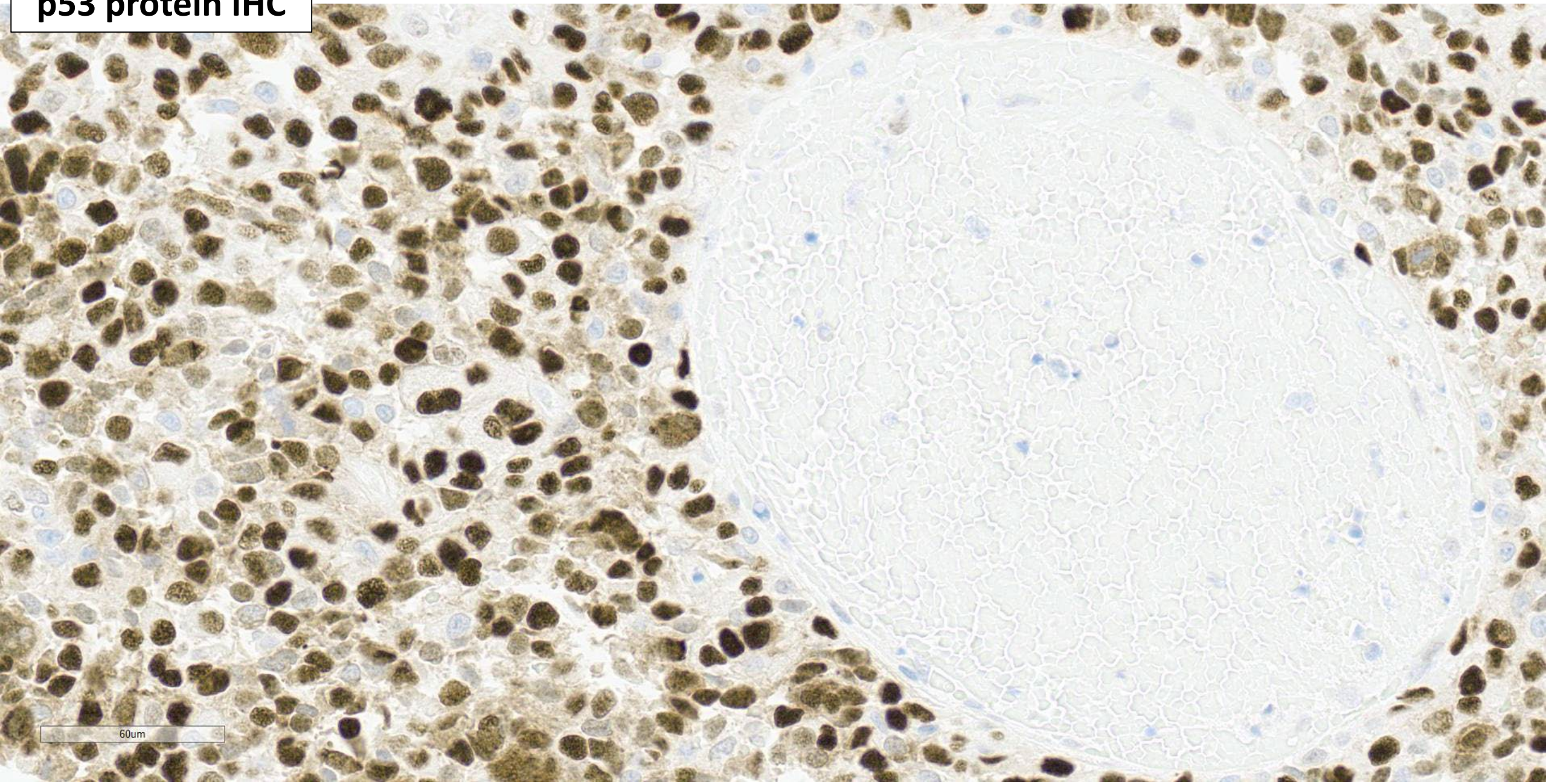
p53 protein IHC
(whole mount)



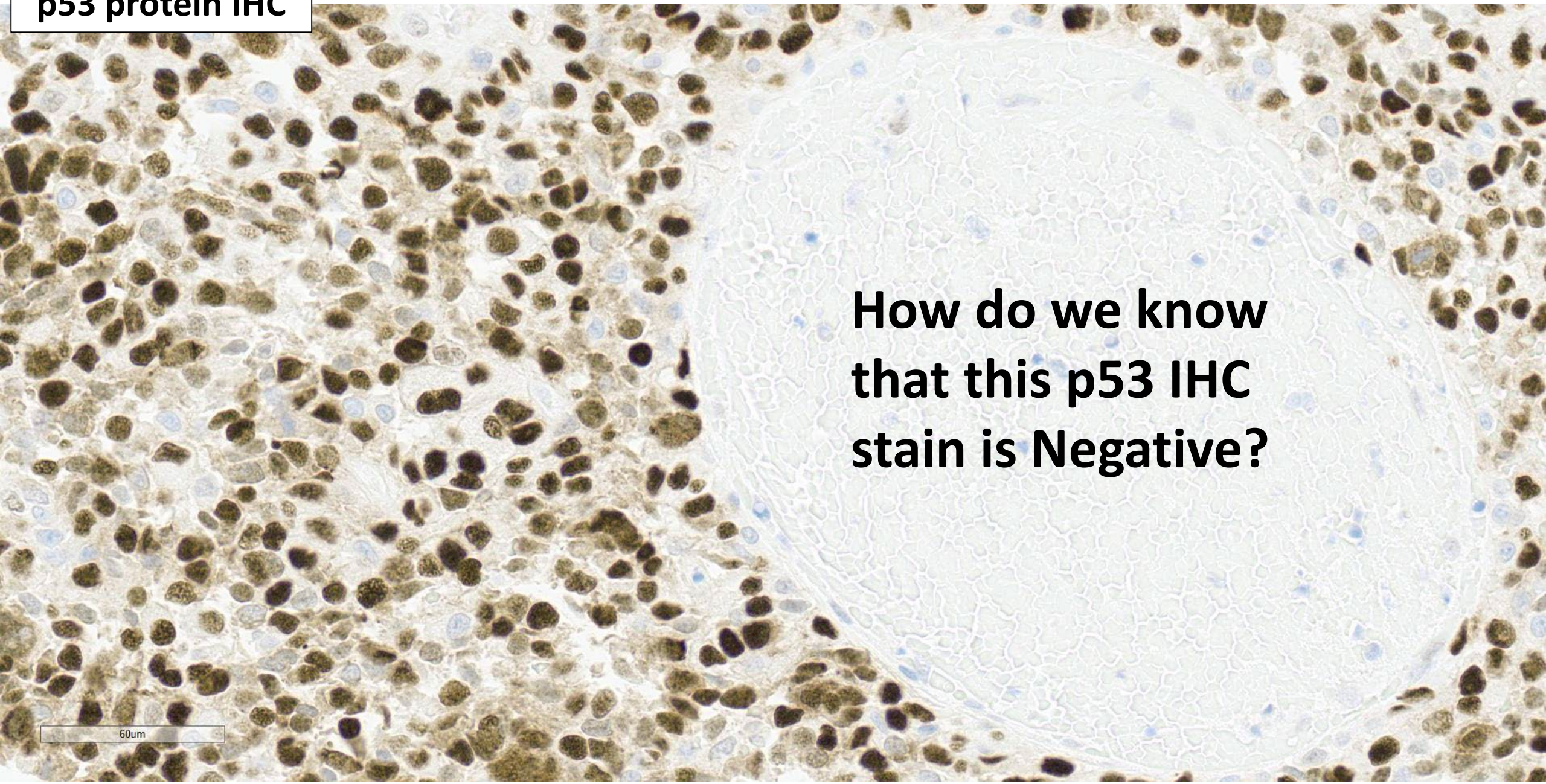
p53 protein IHC



p53 protein IHC



p53 protein IHC

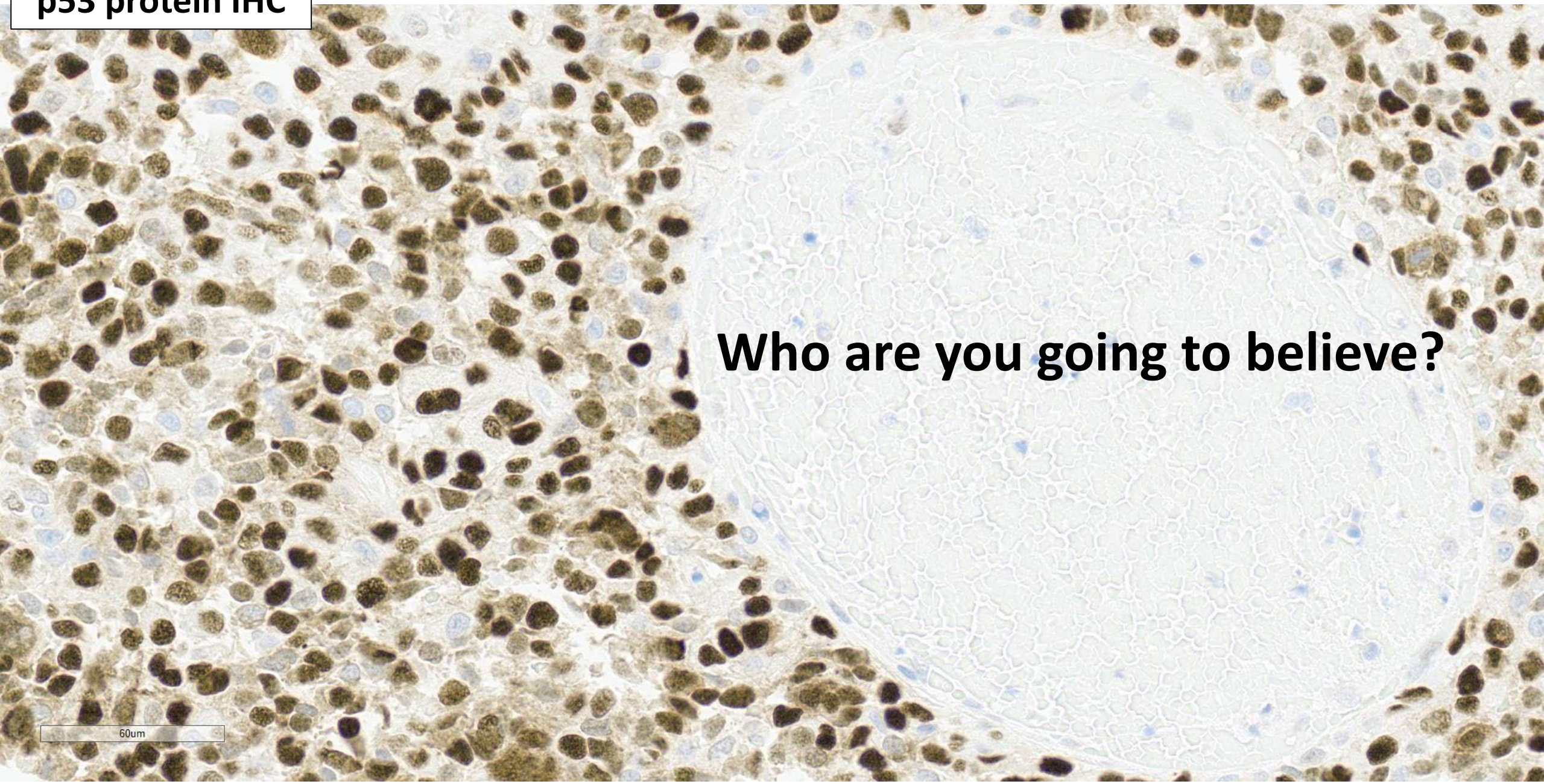


How do we know that this p53 IHC stain is Negative?

Referring Institution Path Report

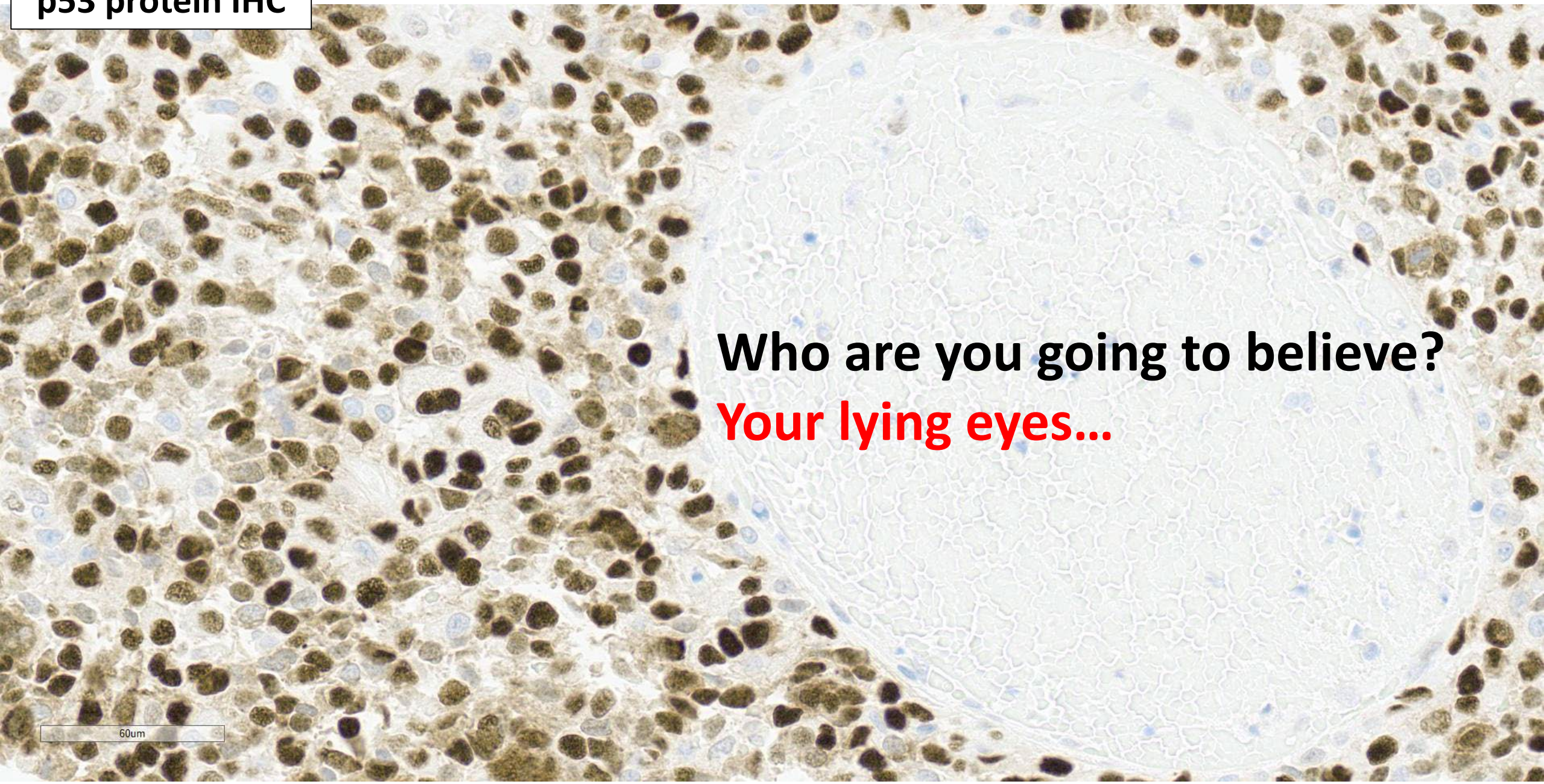
"p53: NEGATIVE"

p53 protein IHC



Who are you going to believe?

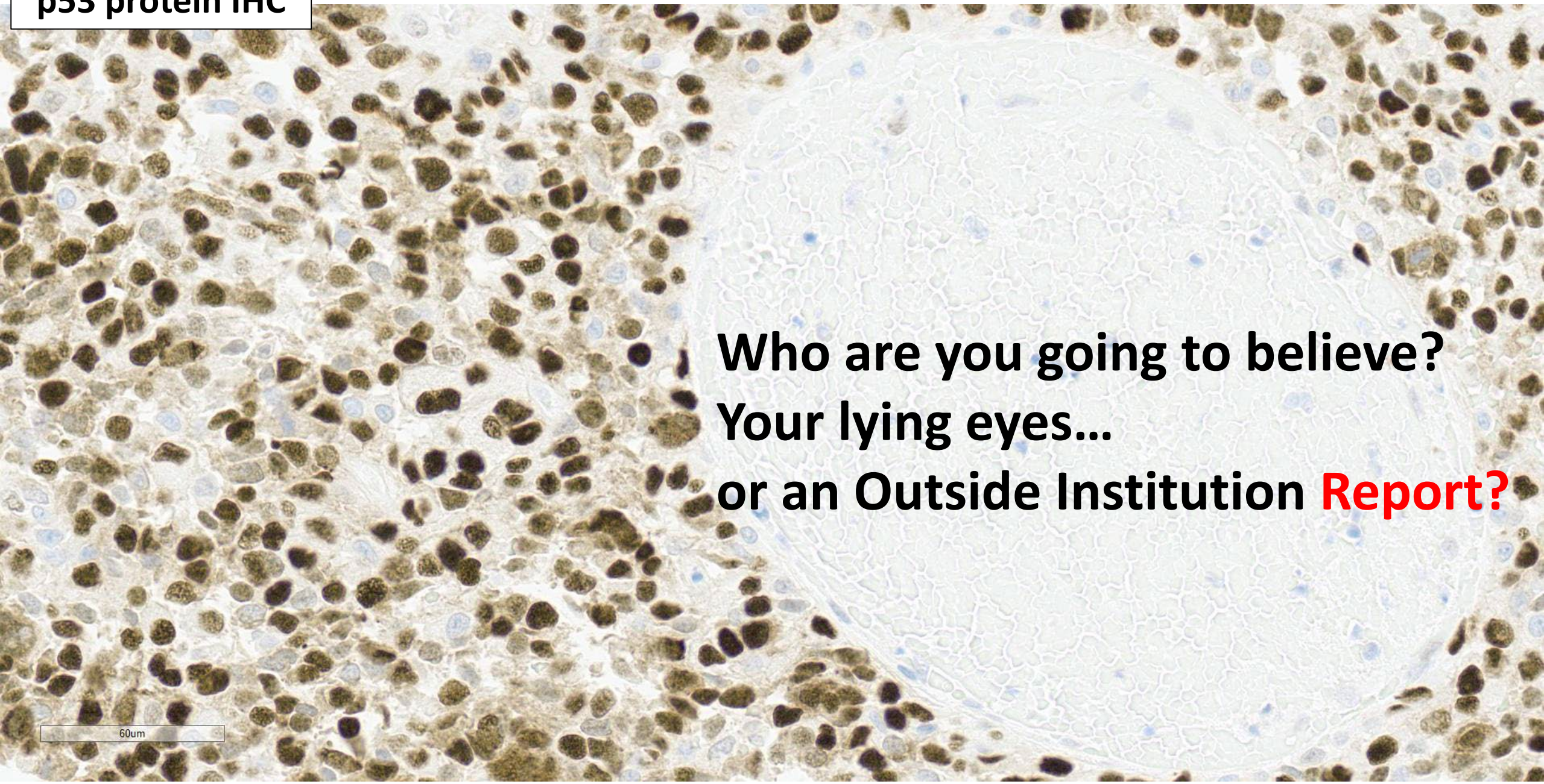
p53 protein IHC



Who are you going to believe?

Your lying eyes…

p53 protein IHC



Who are you going to believe?
Your lying eyes…
or an Outside Institution Report?

p53 protein IHC

WE MUST EVALUATE

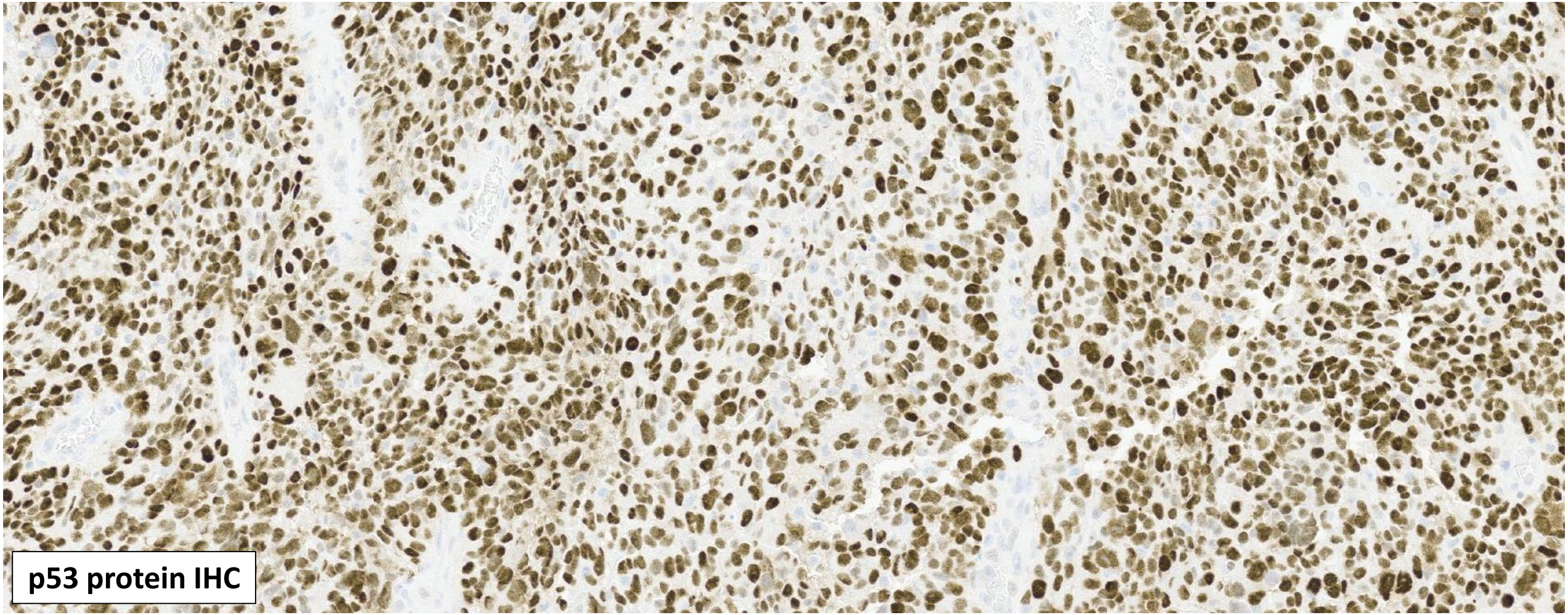
DATA

NOT OSI REPORTS!

GLIOBLASTOMA, IDH-WILDTYPE
CNS WHO GRADE 4

MDACC Path Report

IDH1 protein status (IHC): NEGATIVE for p.R132H expression
p53 protein status (IHC): POSITIVE for nuclear expression (strong, diffuse, 95%; indicative of *TP53* mutation)
EGFR protein status (IHC): POSITIVE (strong, diffuse, membranous pattern)



p53 protein IHC

For the Residents and Fellows…

OSI Dx: Minimum

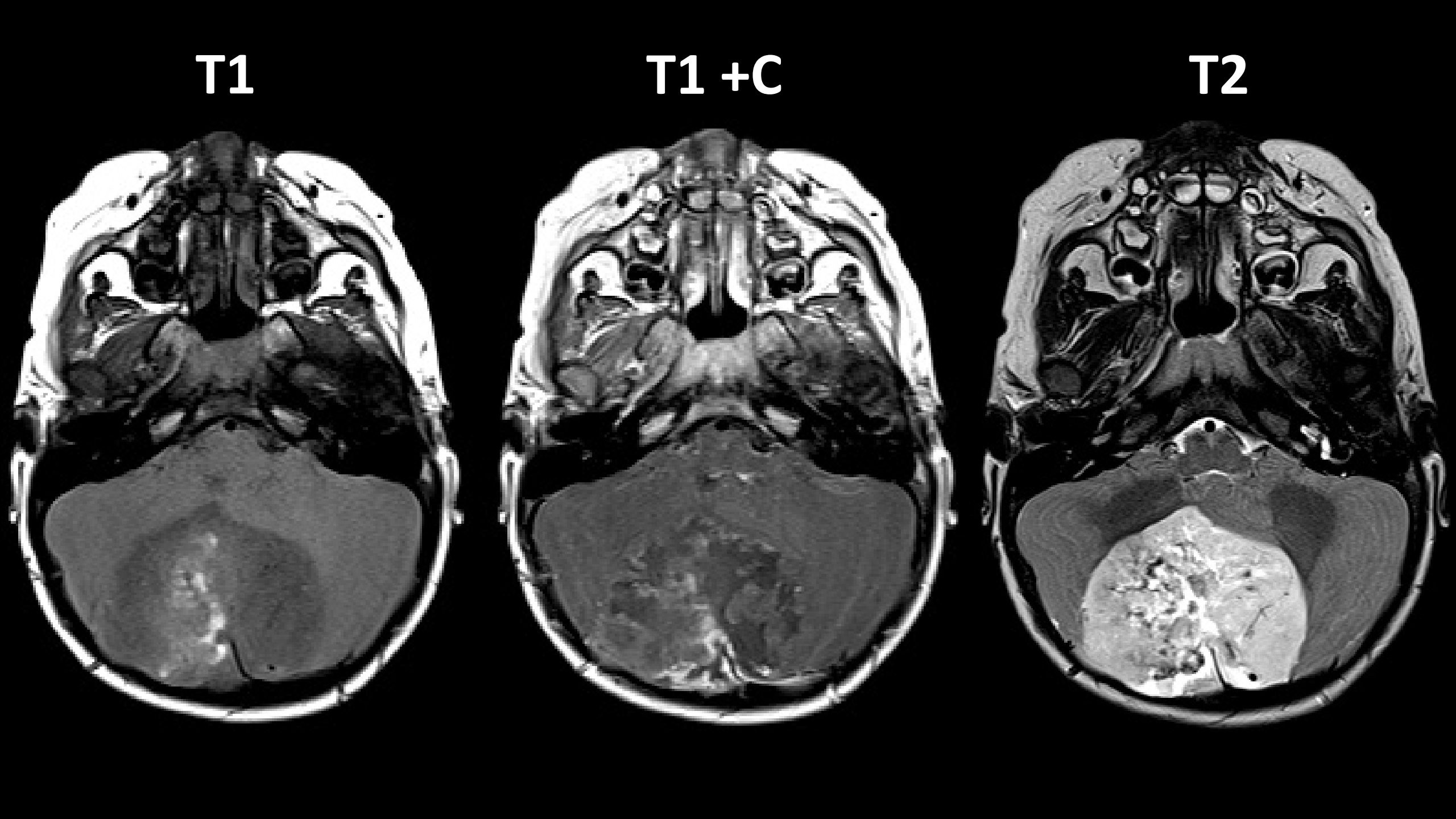
8%

Serious Discrepancy

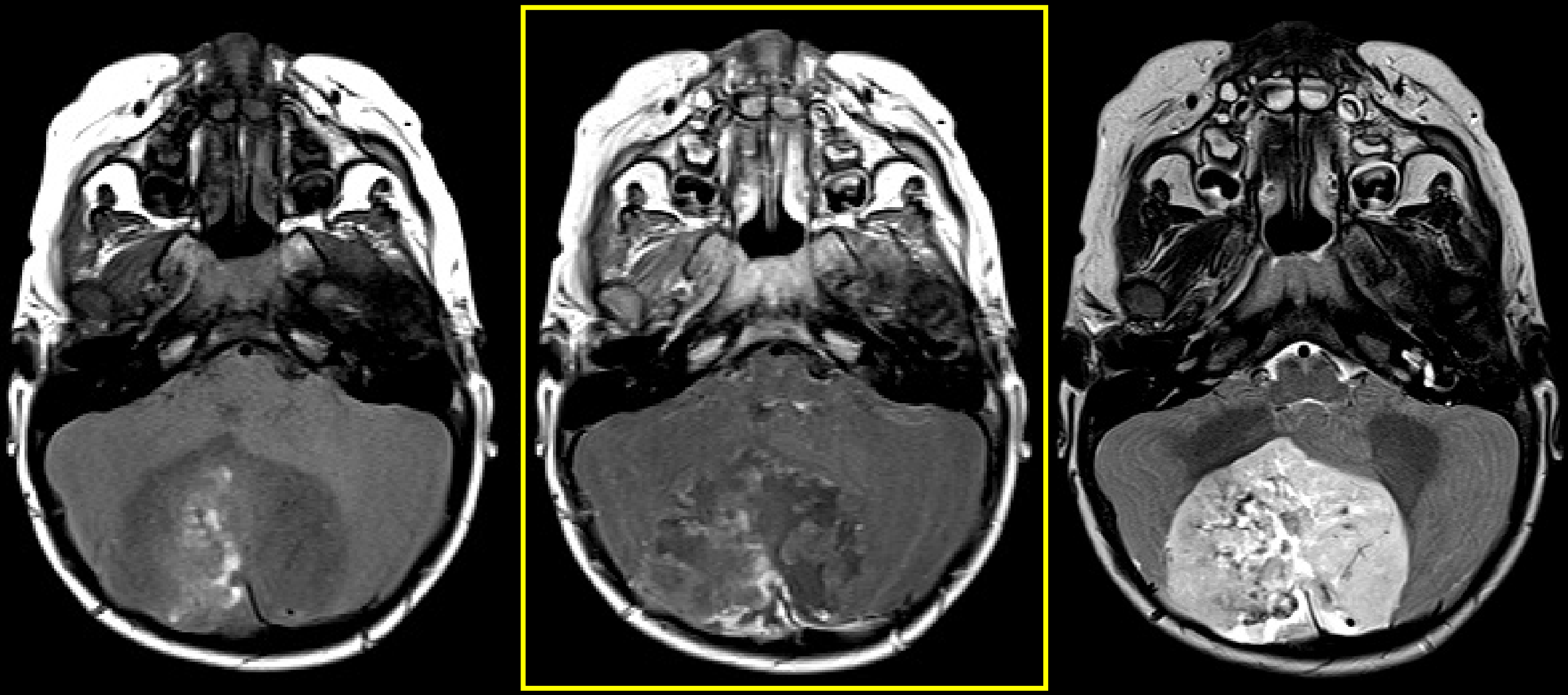
So … if you are not identifying errors in …

Patient 4

1-year-old female

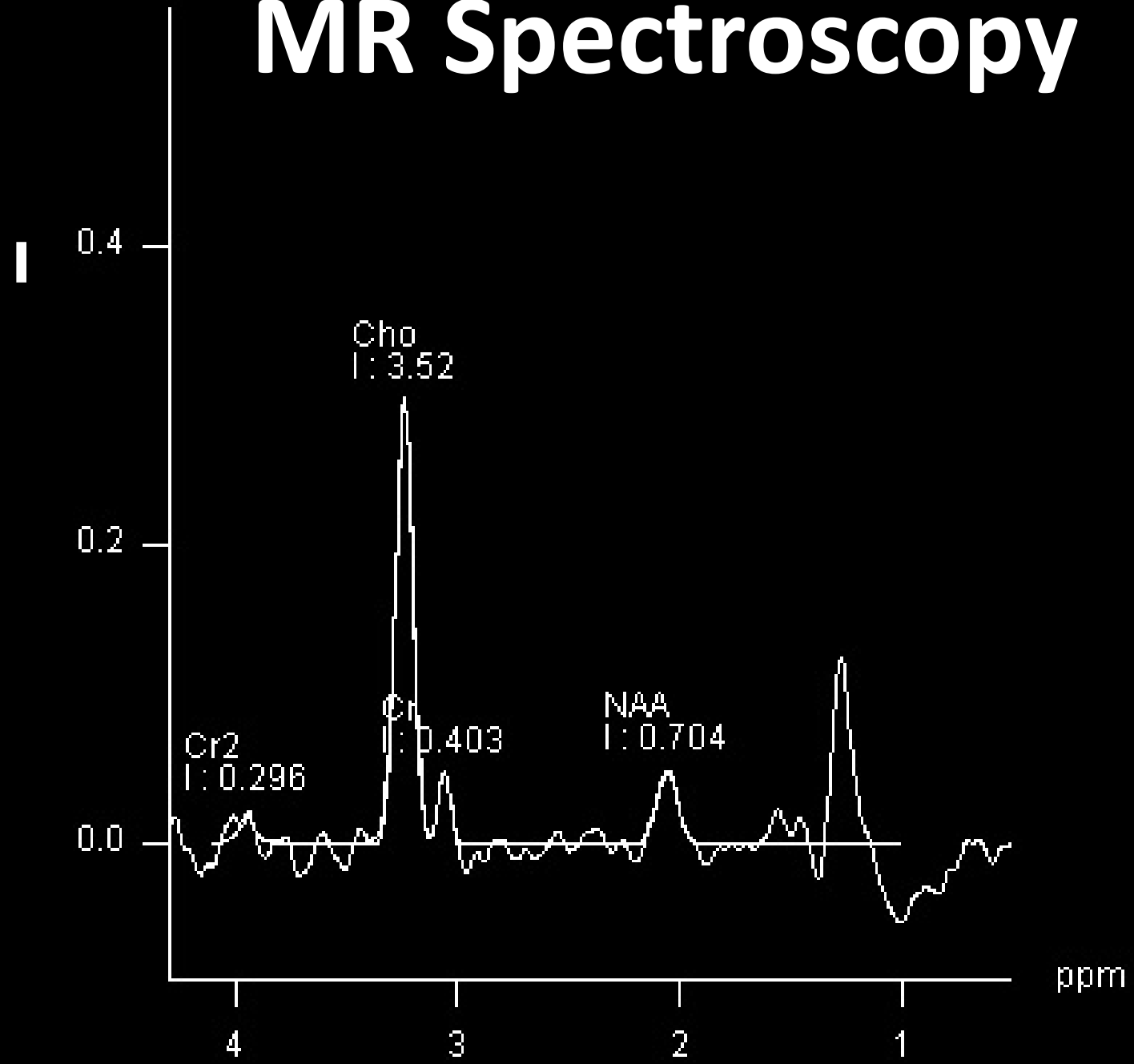

T1
T1 +C
T2

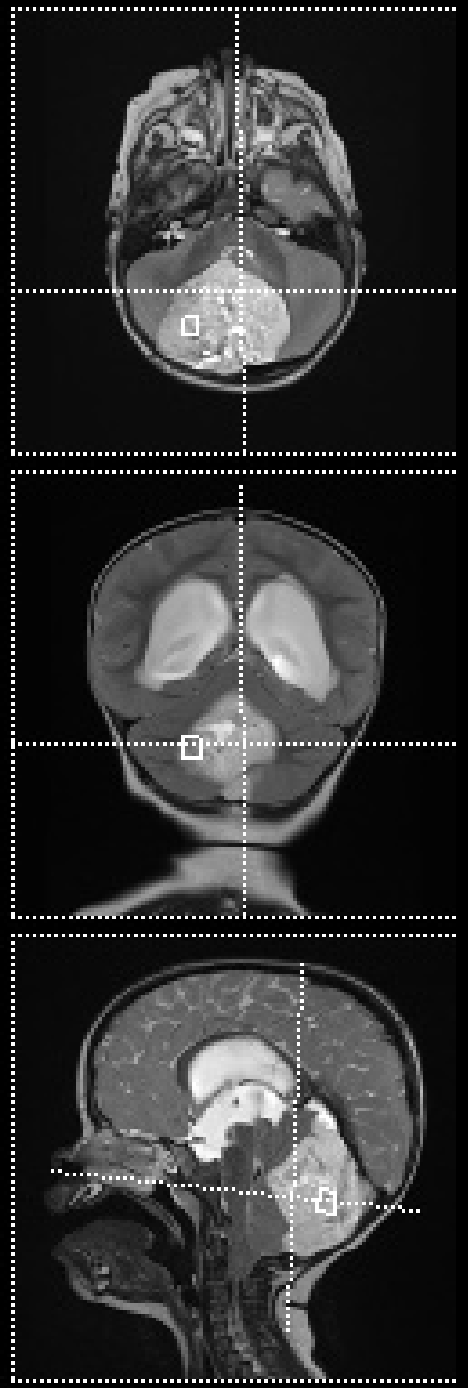
Note: *Very Poor* Contrast Uptake



Prominent Internal Veins!

MR Spectroscopy





Proton MR Spectroscopy

MR

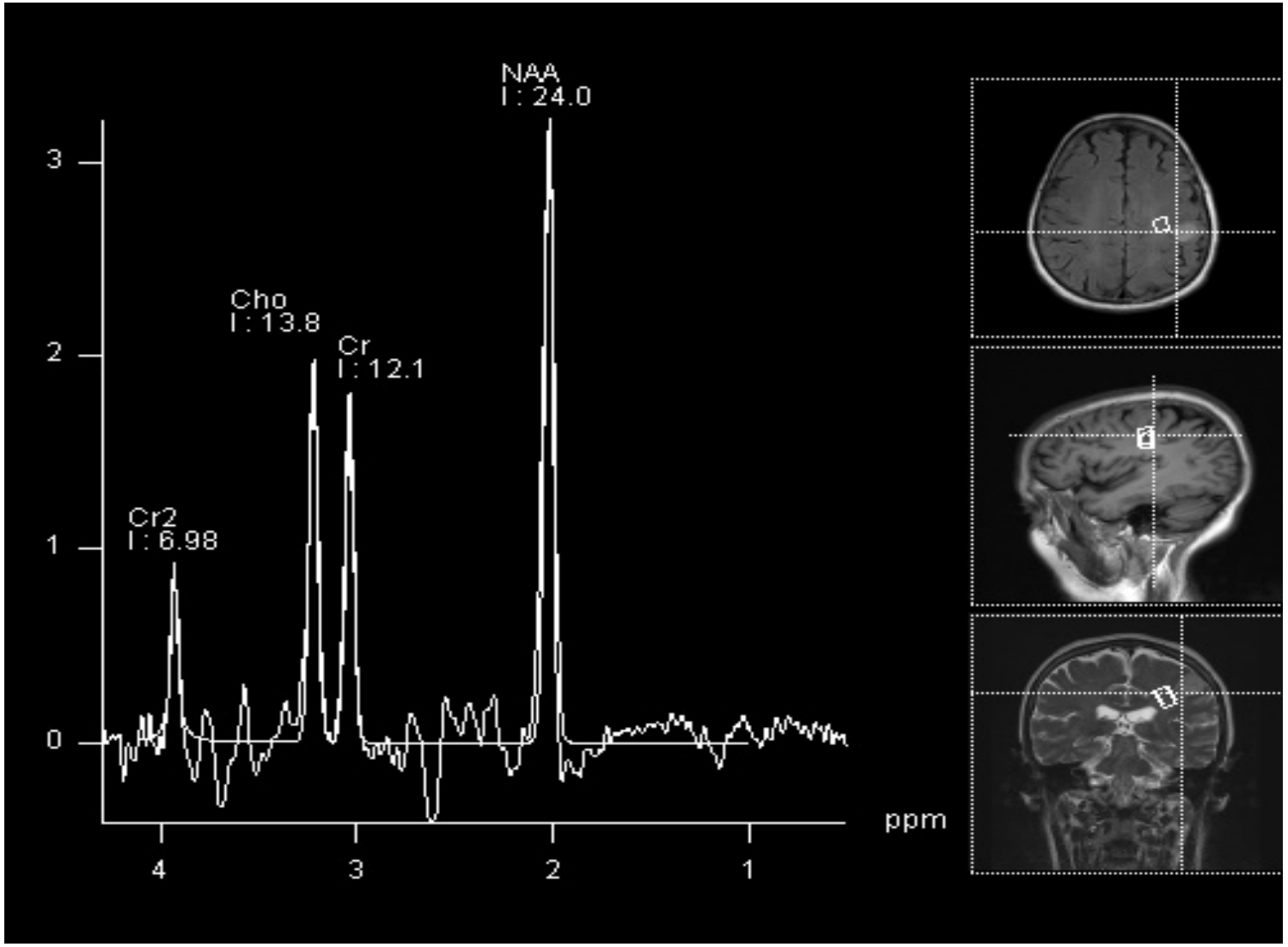
Spectroscopy

MRS

Measurable Proton Metabolites

• Choline	3.2 ppm
• Creatine	3.0 ppm
• NAA	2.0 ppm
• Lipid/Lactate	0.9-1.4

MR Spectroscopy



Proton MR Spectroscopy

Up is good (normal)

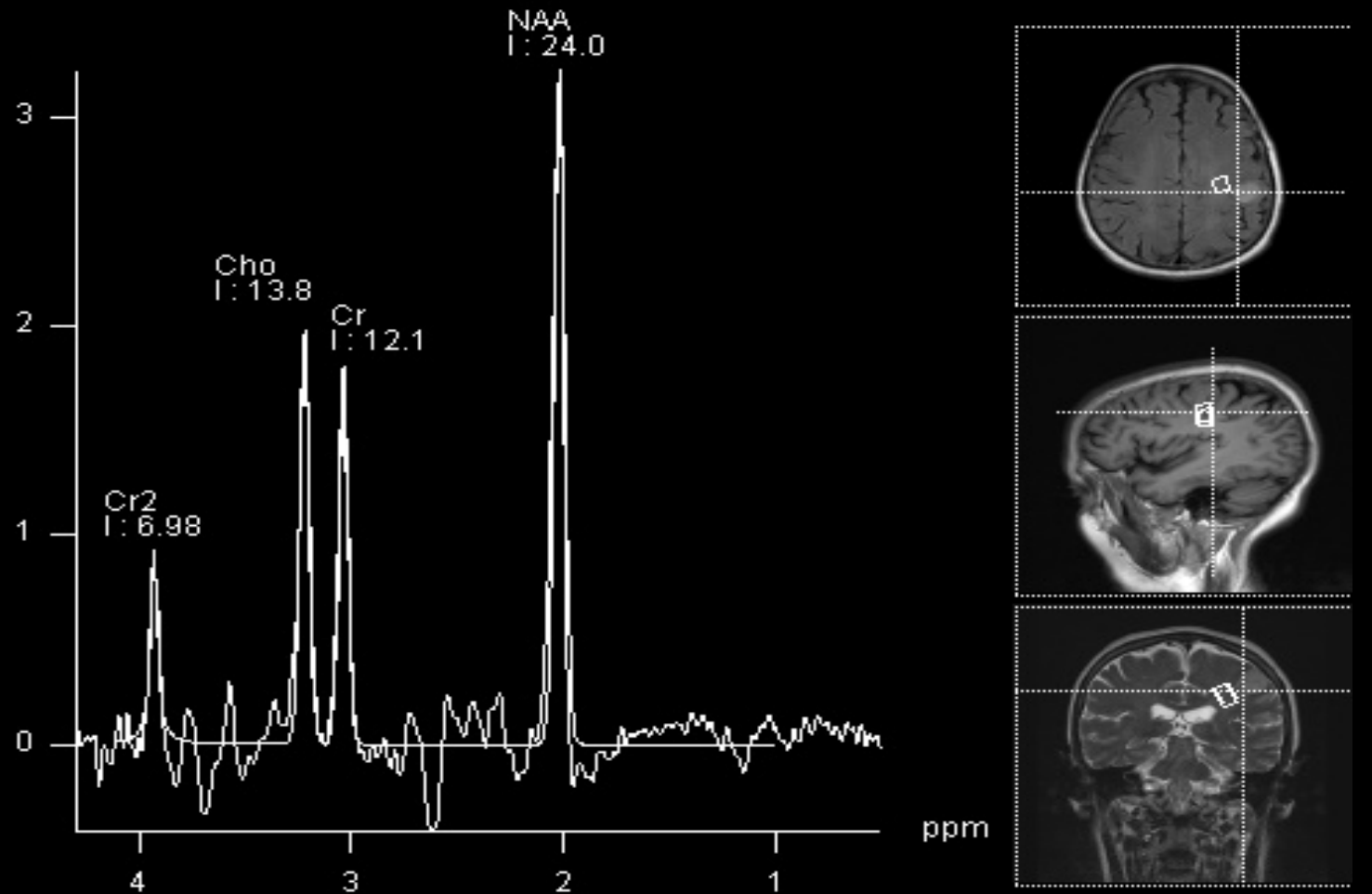
Down is bad (tumor)

Proton MR Spectroscopy

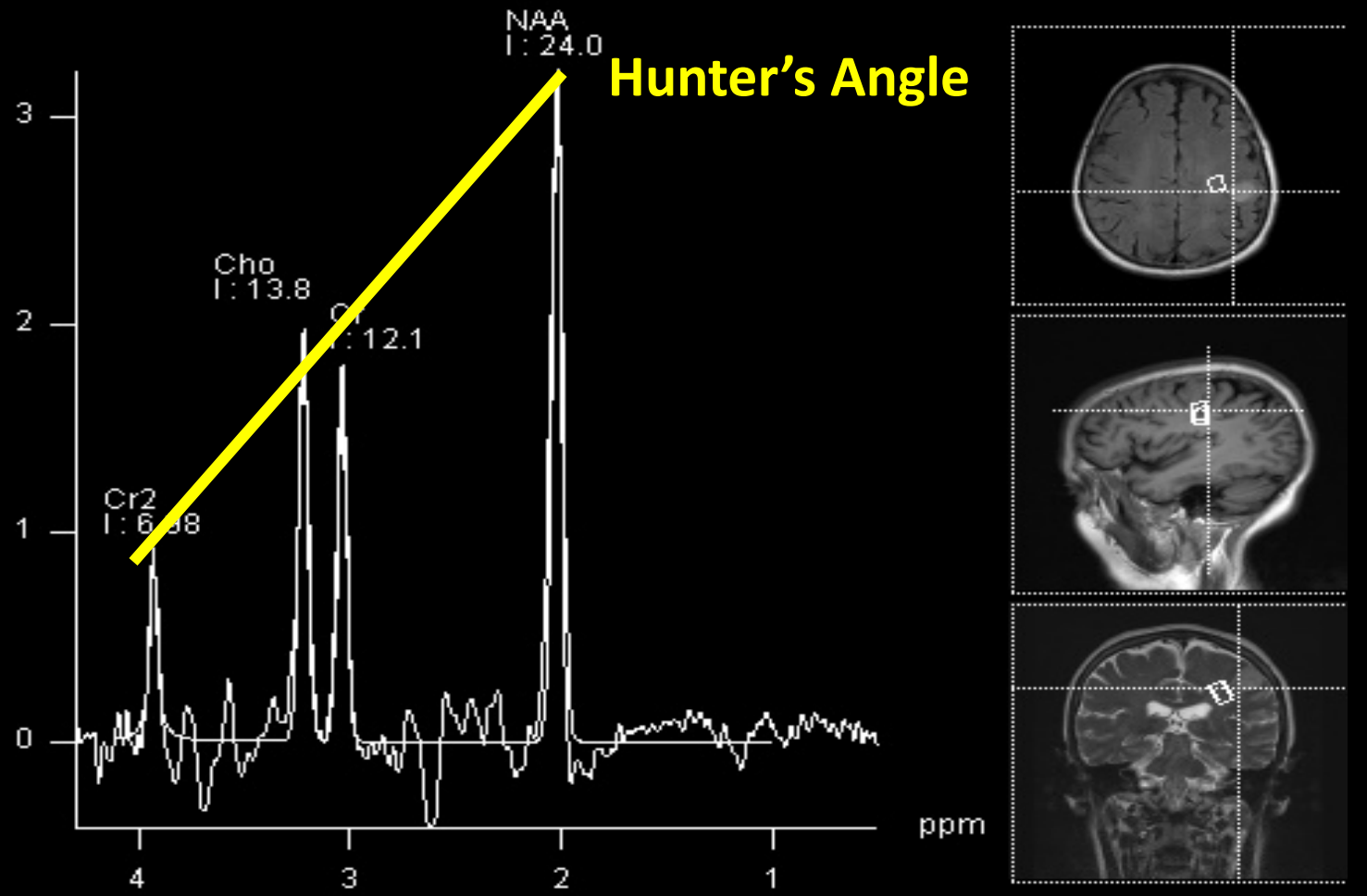
Up is good (normal)

“Up” = Hunter’s Angle = 45° Upslope

Proton MR Spectroscopy



Proton MR Spectroscopy



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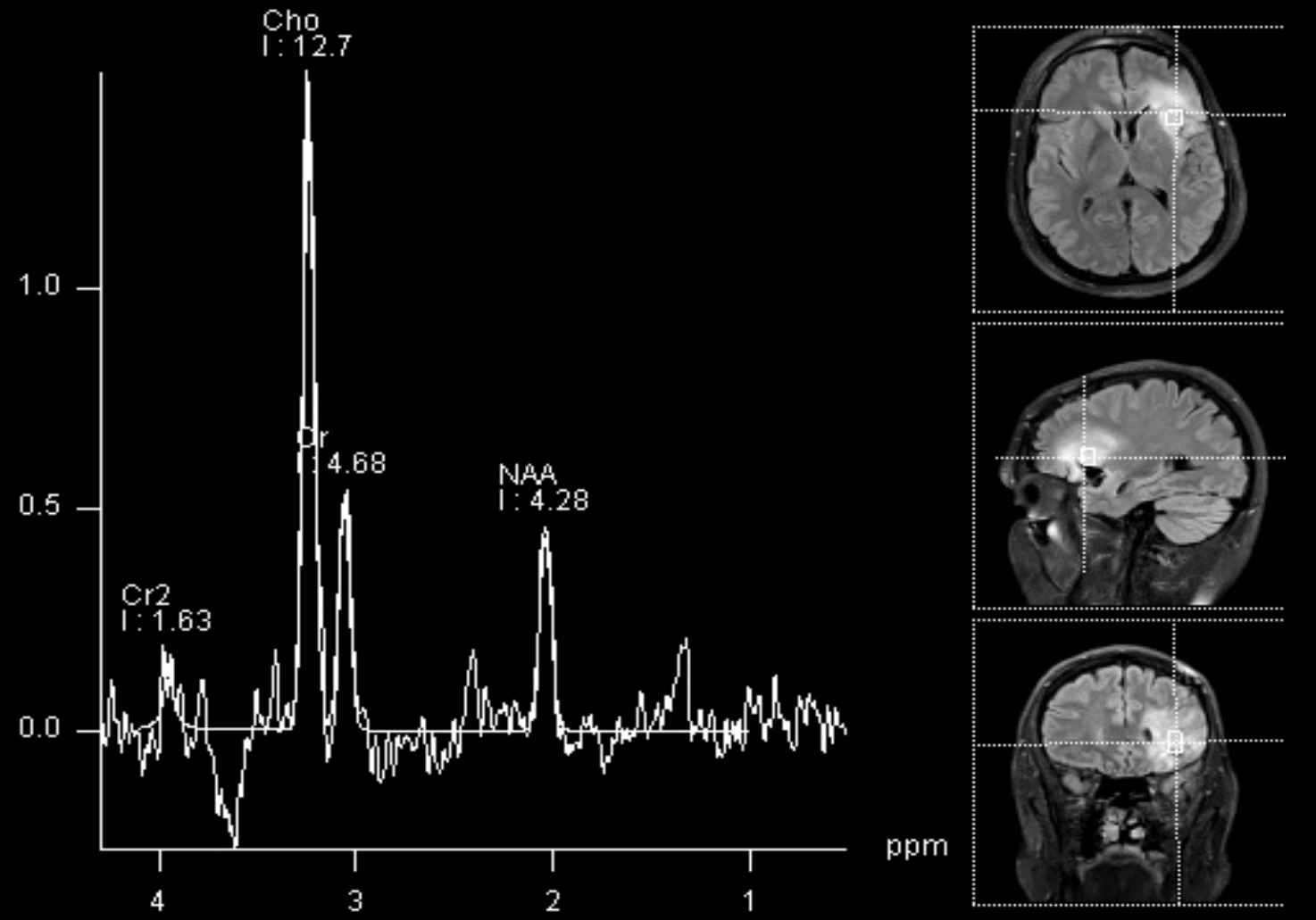

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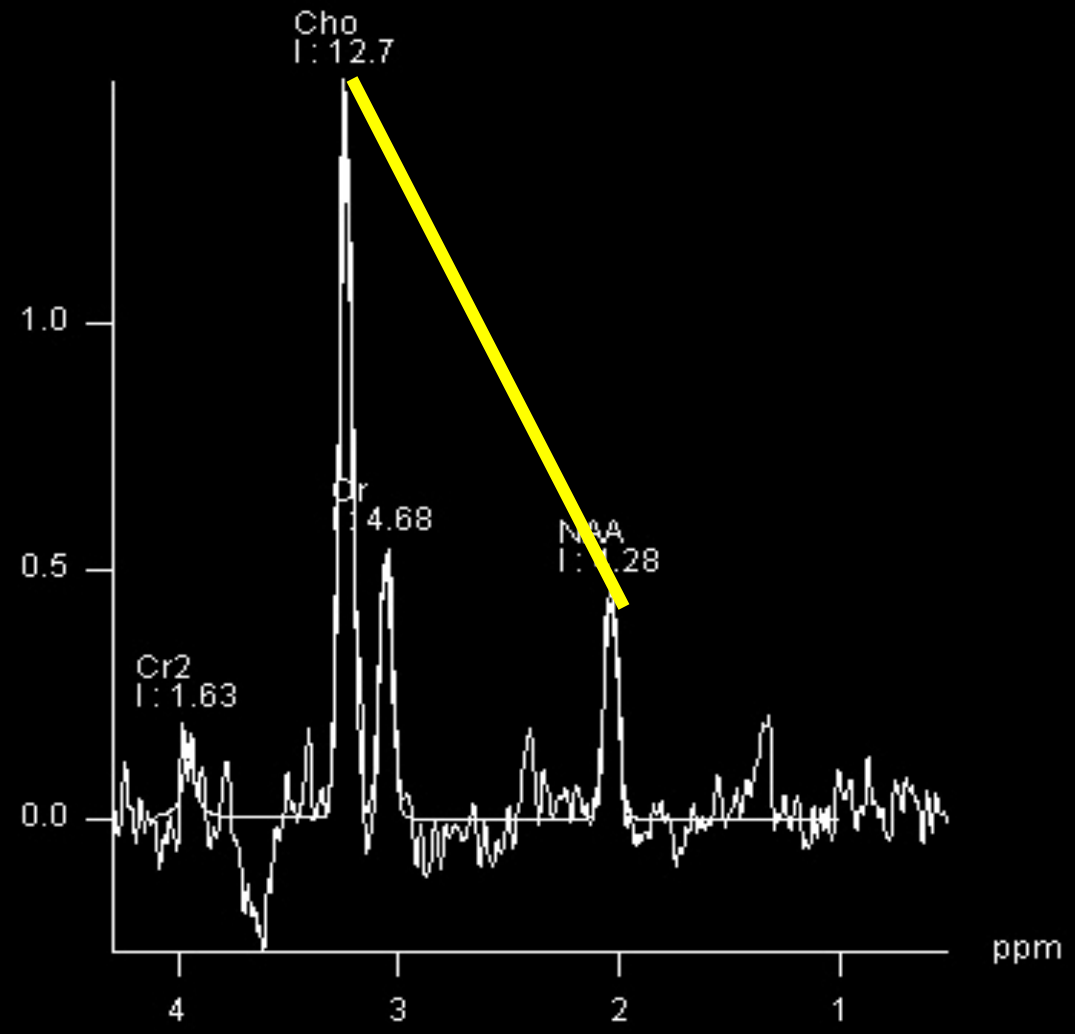
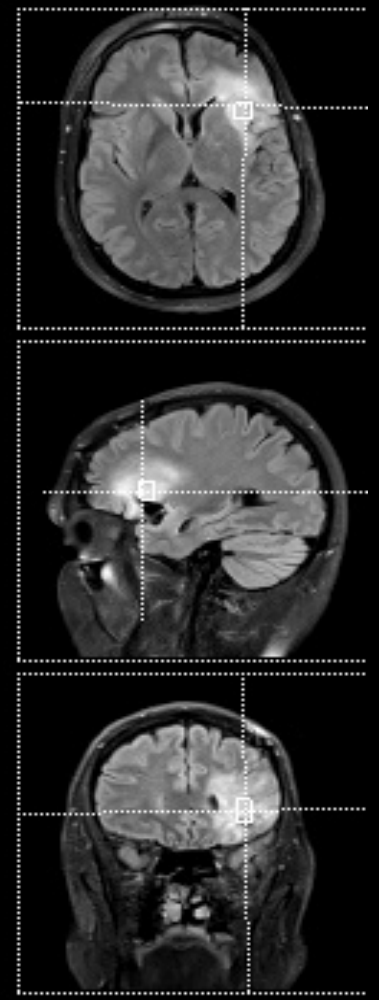
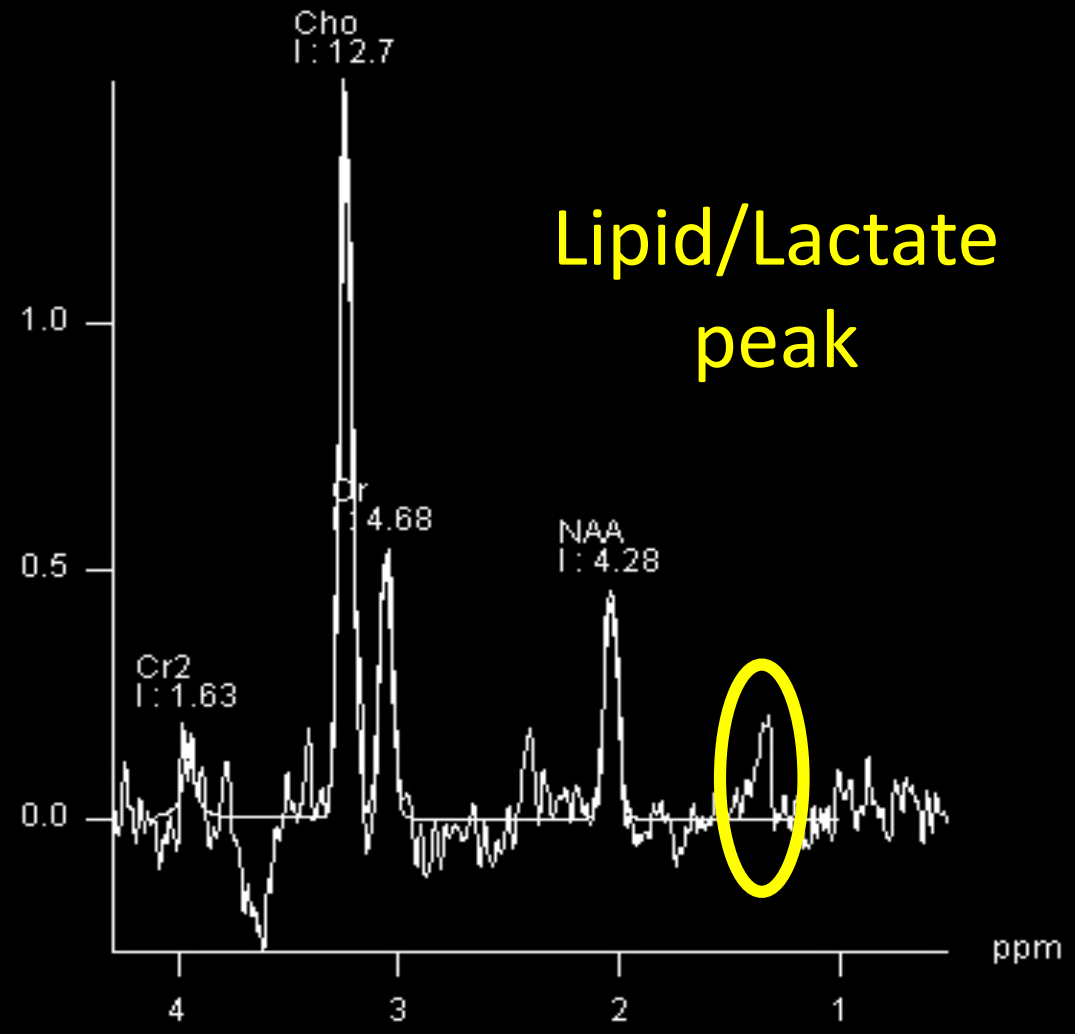
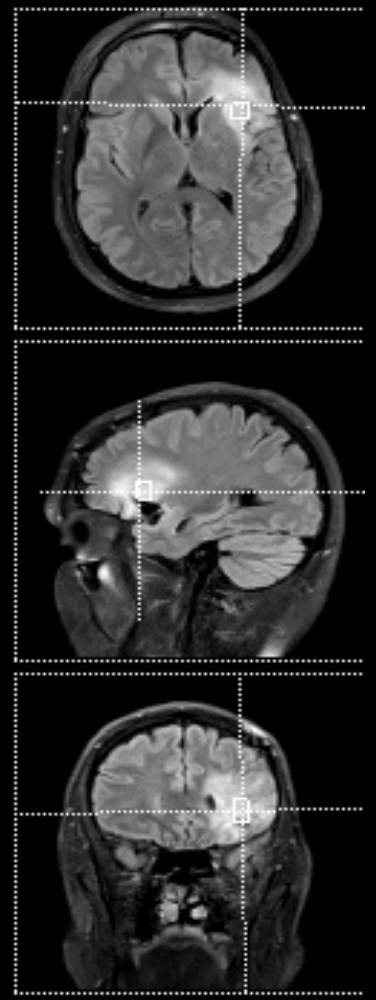




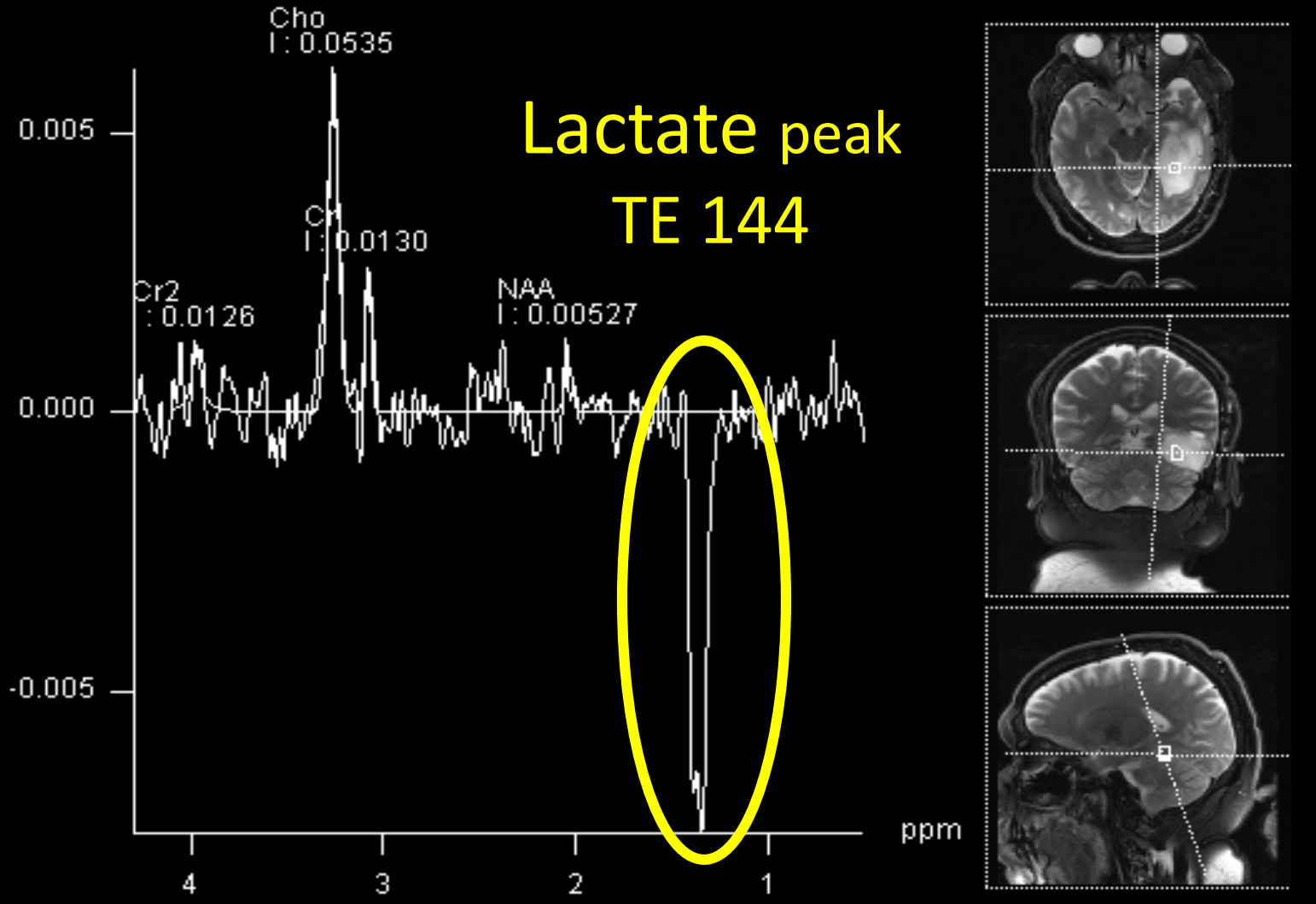
Proton MR Spectroscopy



Lipid/Lactate peak

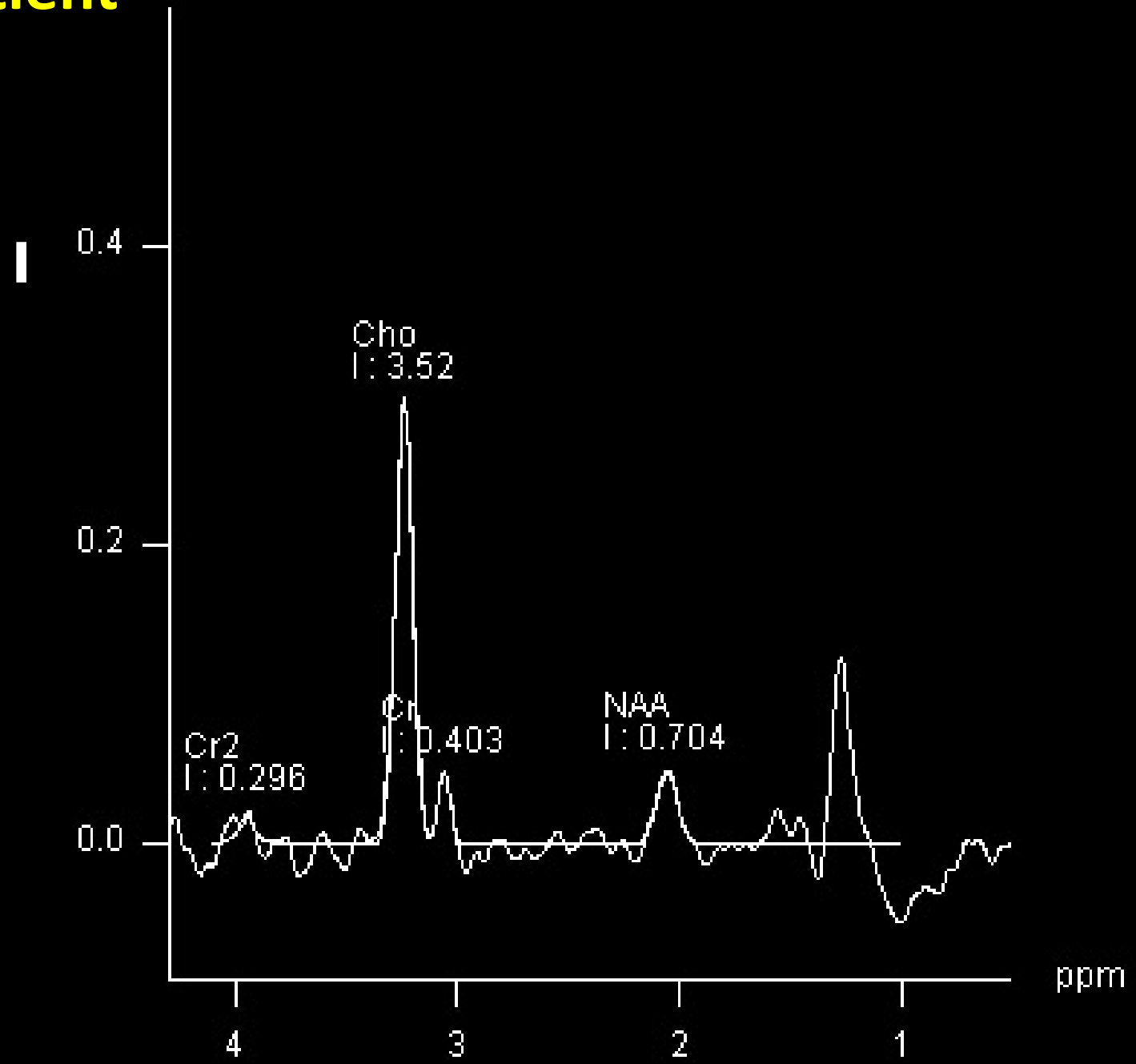


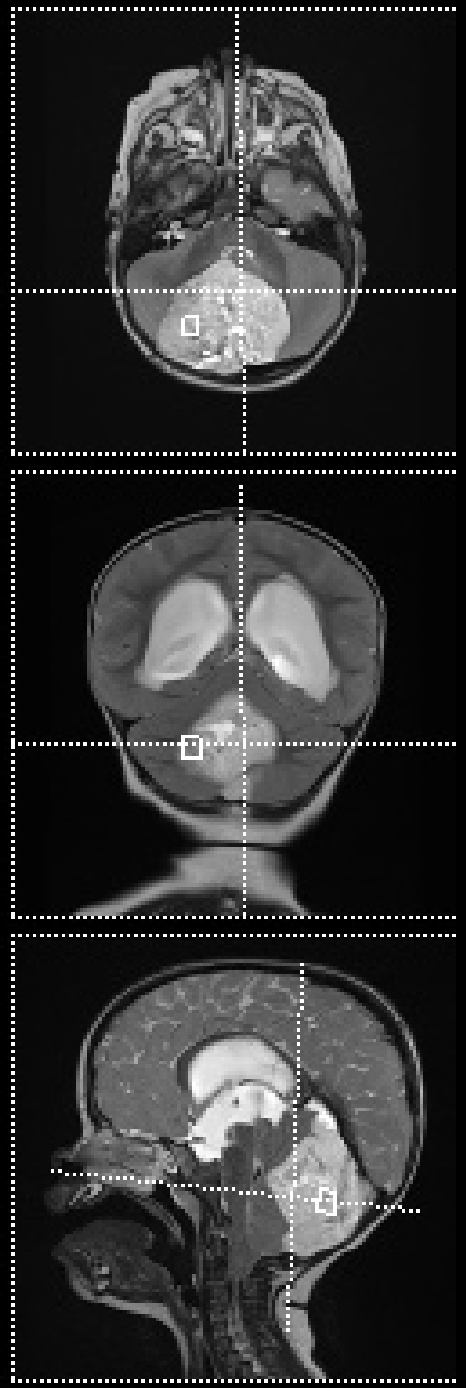
Proton MR Spectroscopy



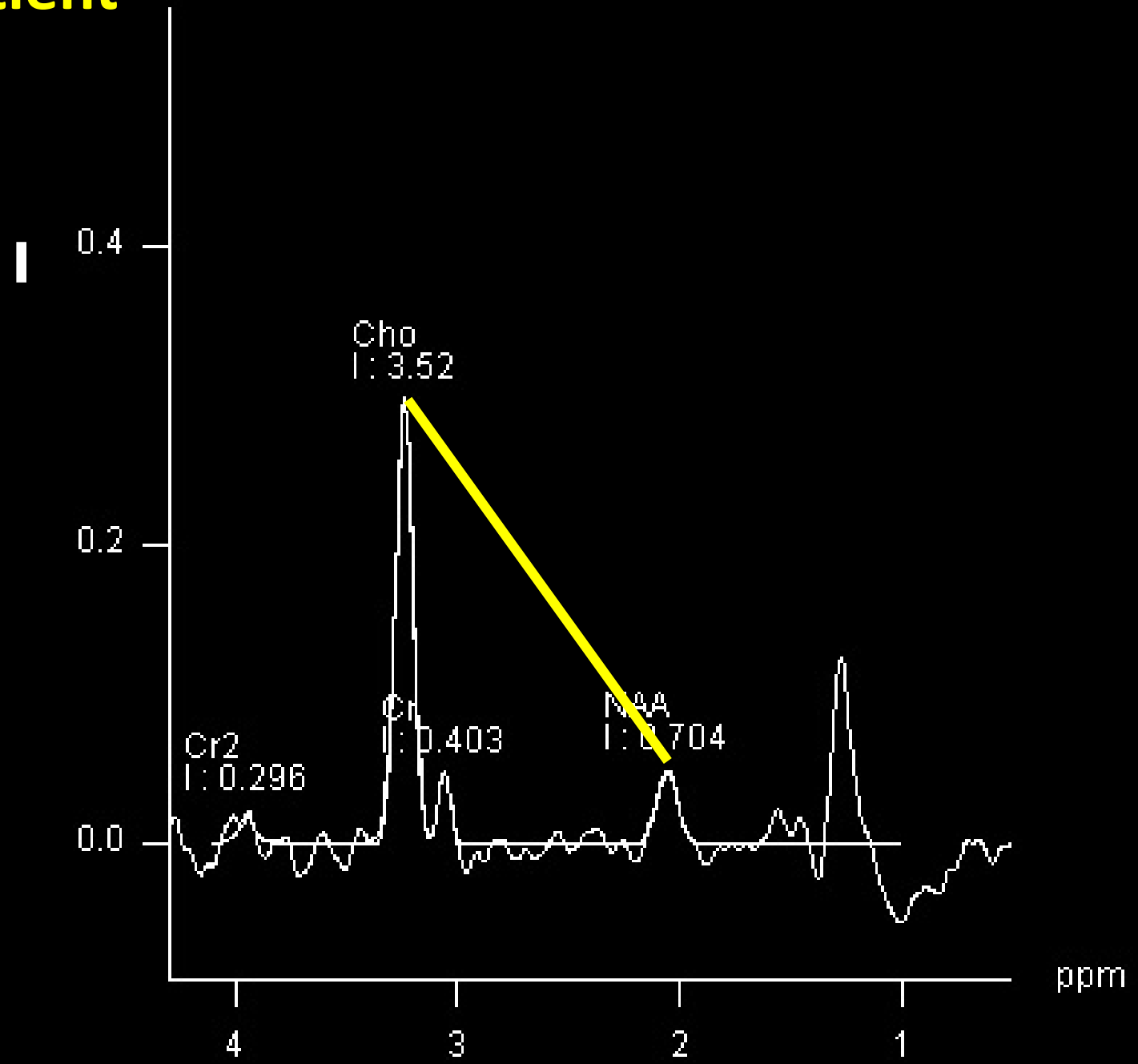
Lactate peak
TE 144

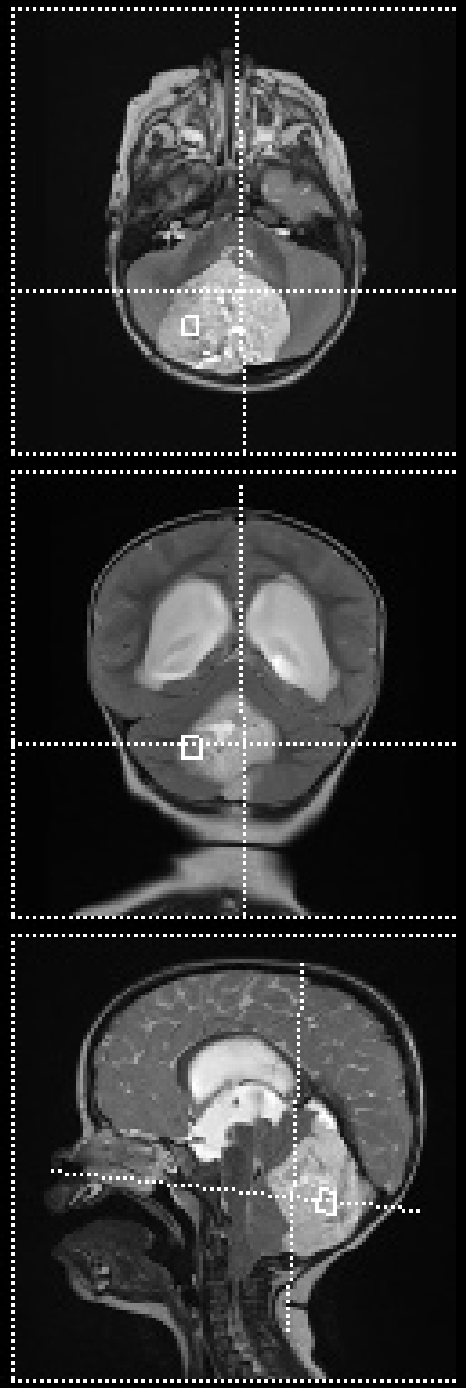
Our patient



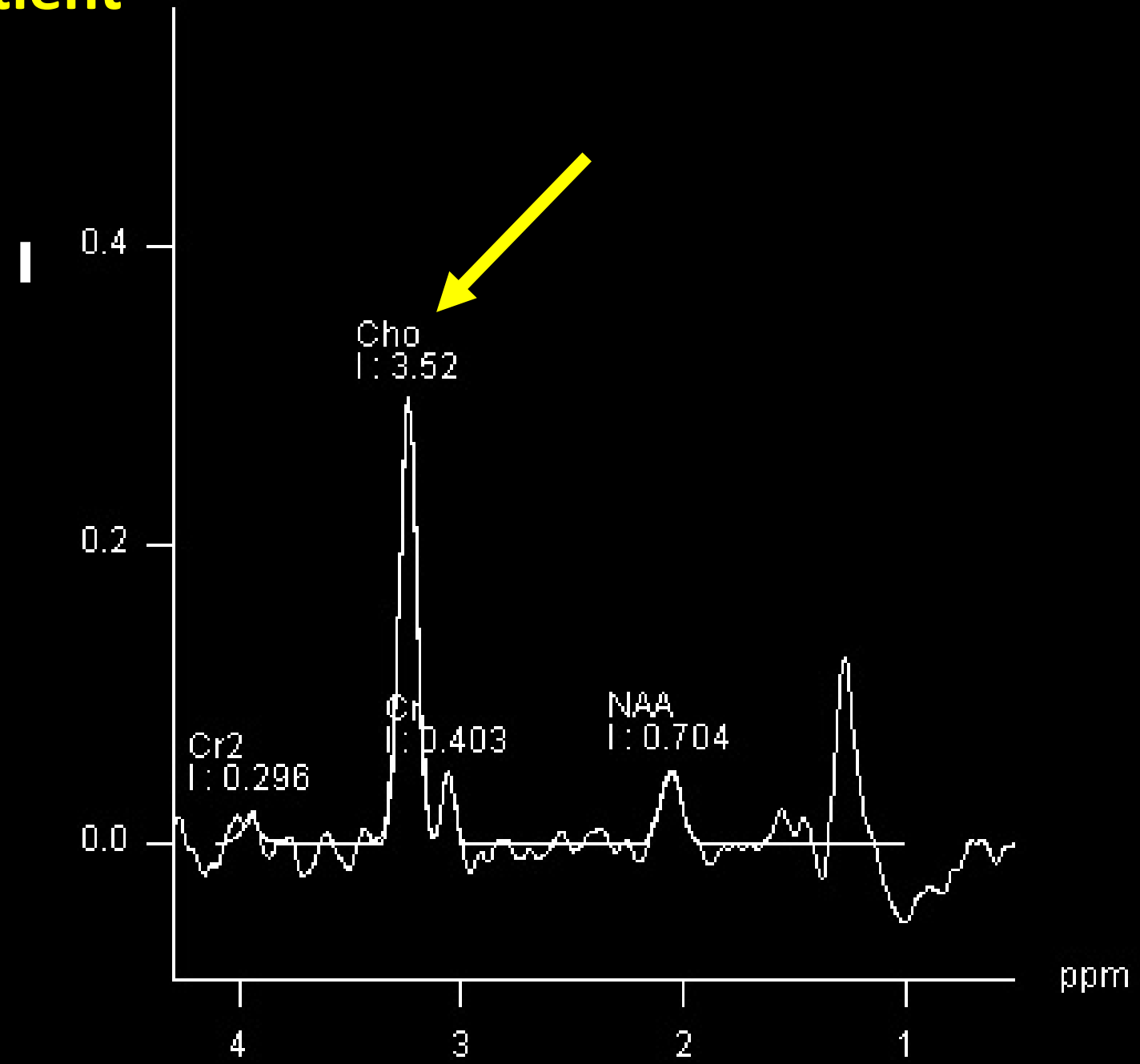


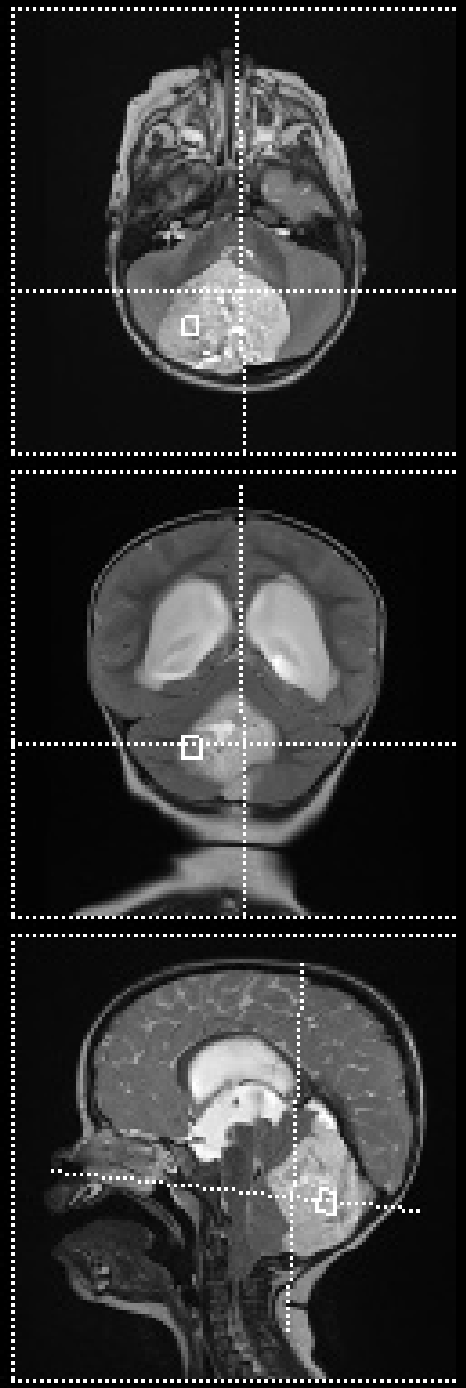
Our patient





Our patient





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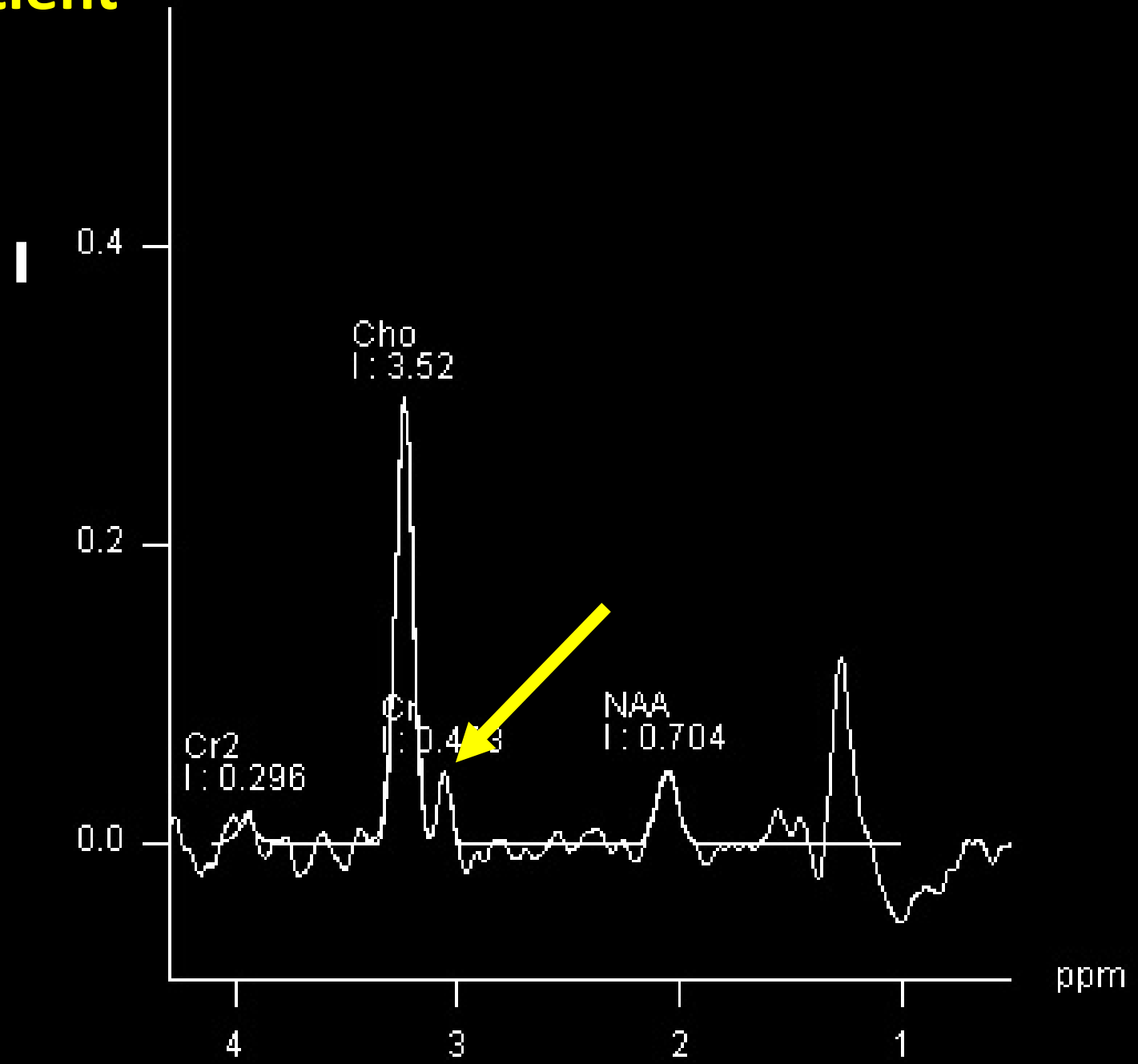

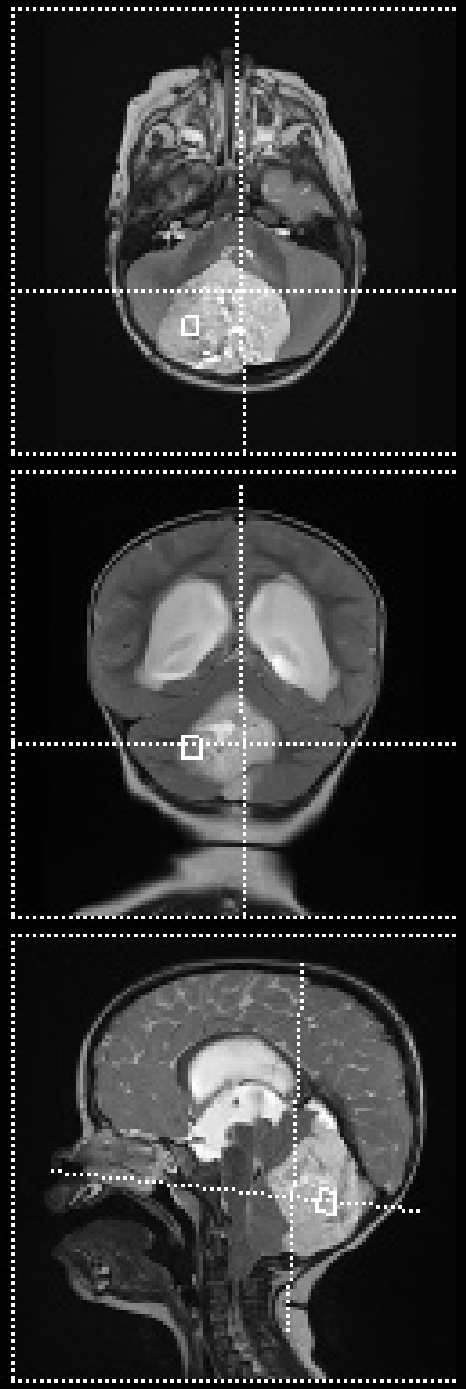

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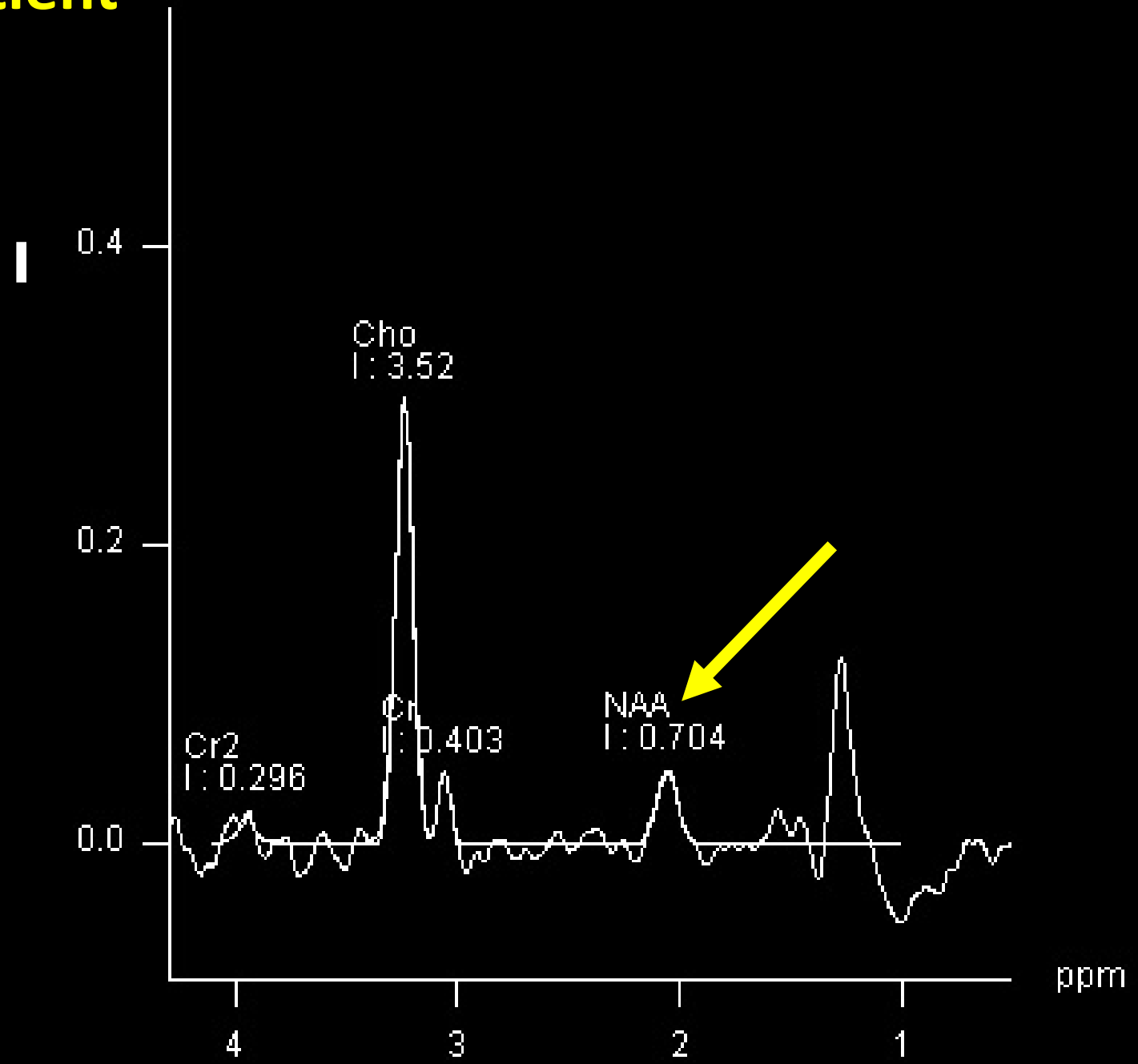

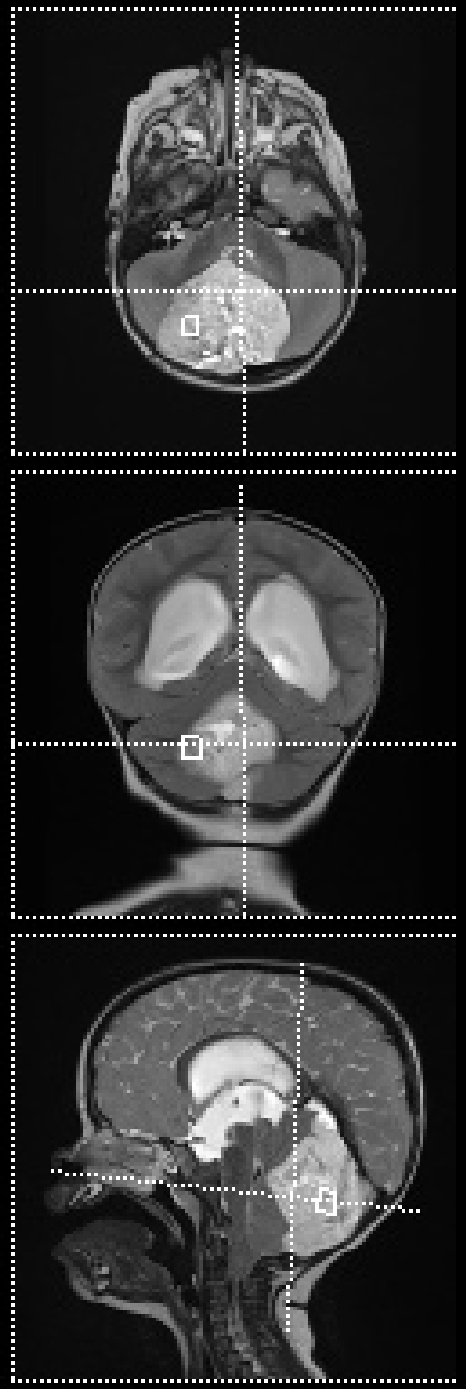

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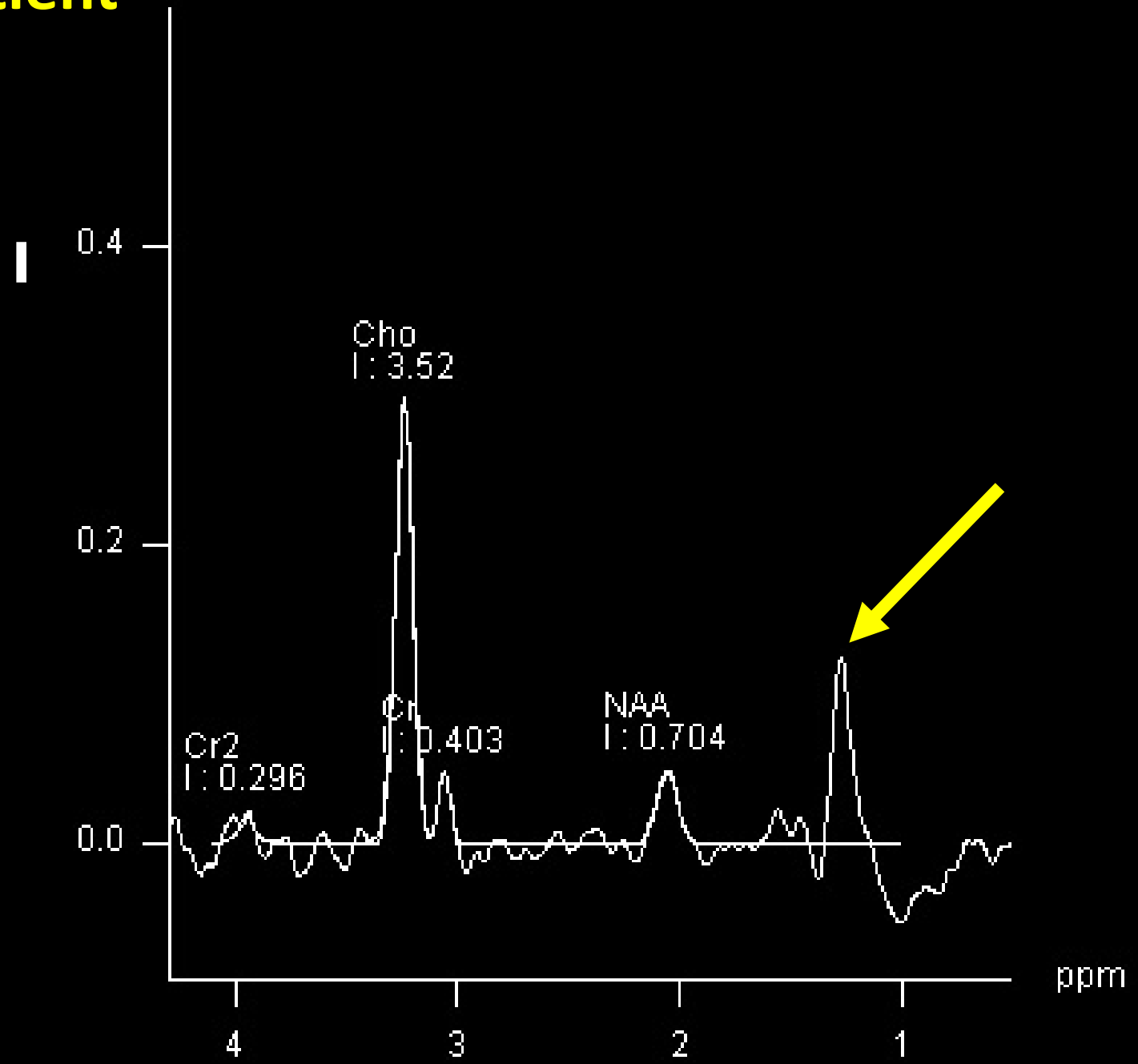
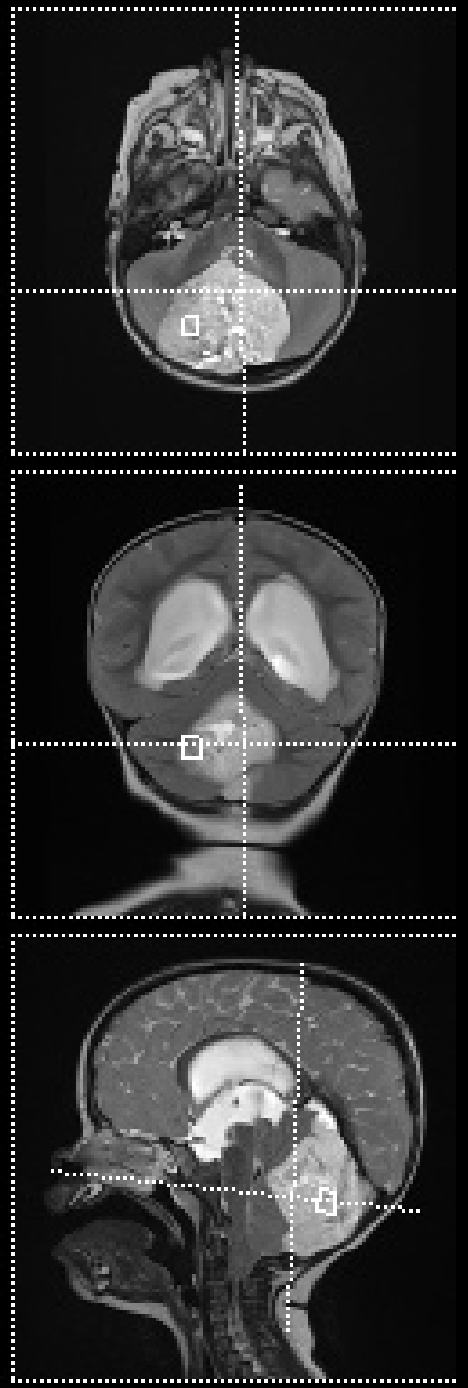
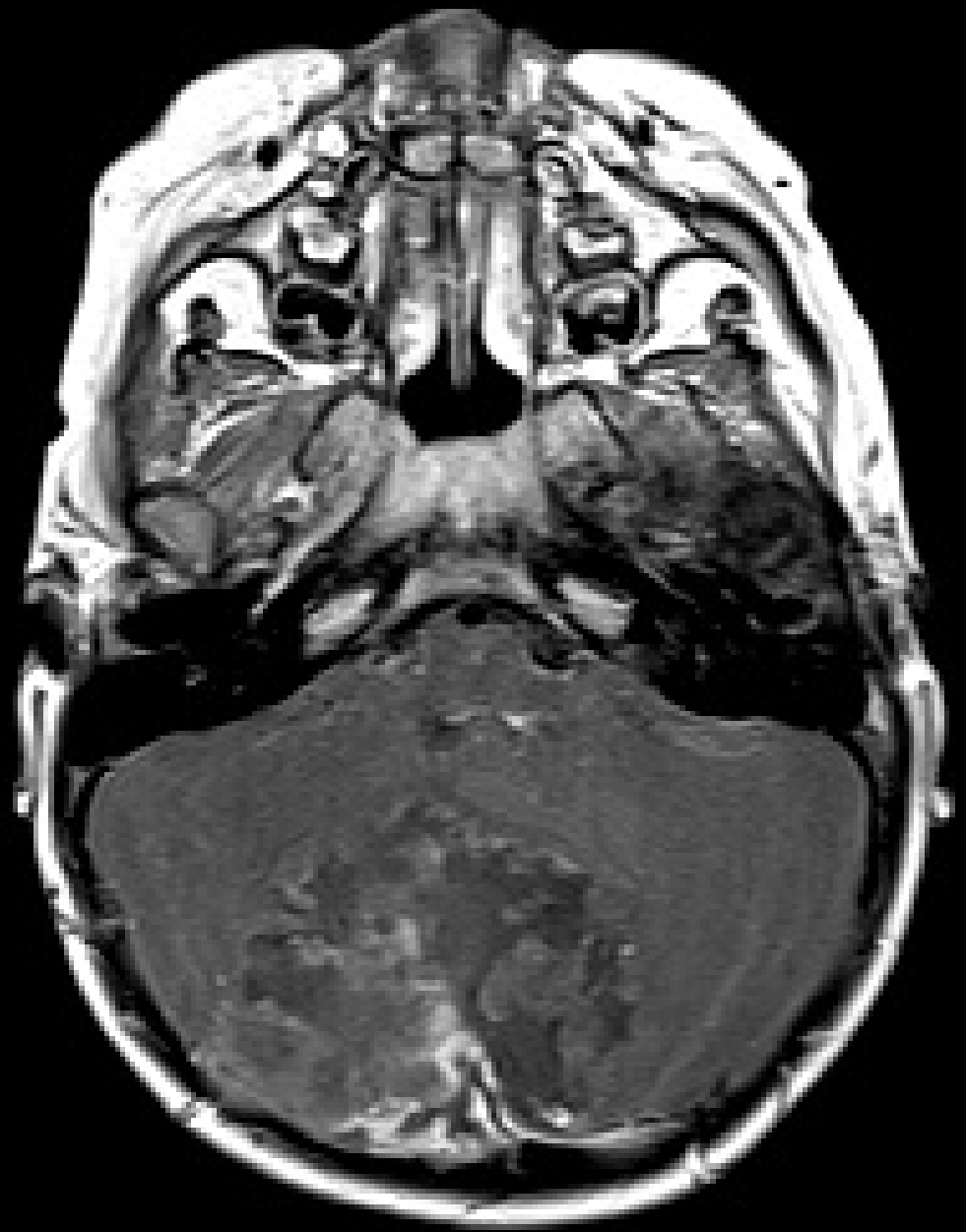
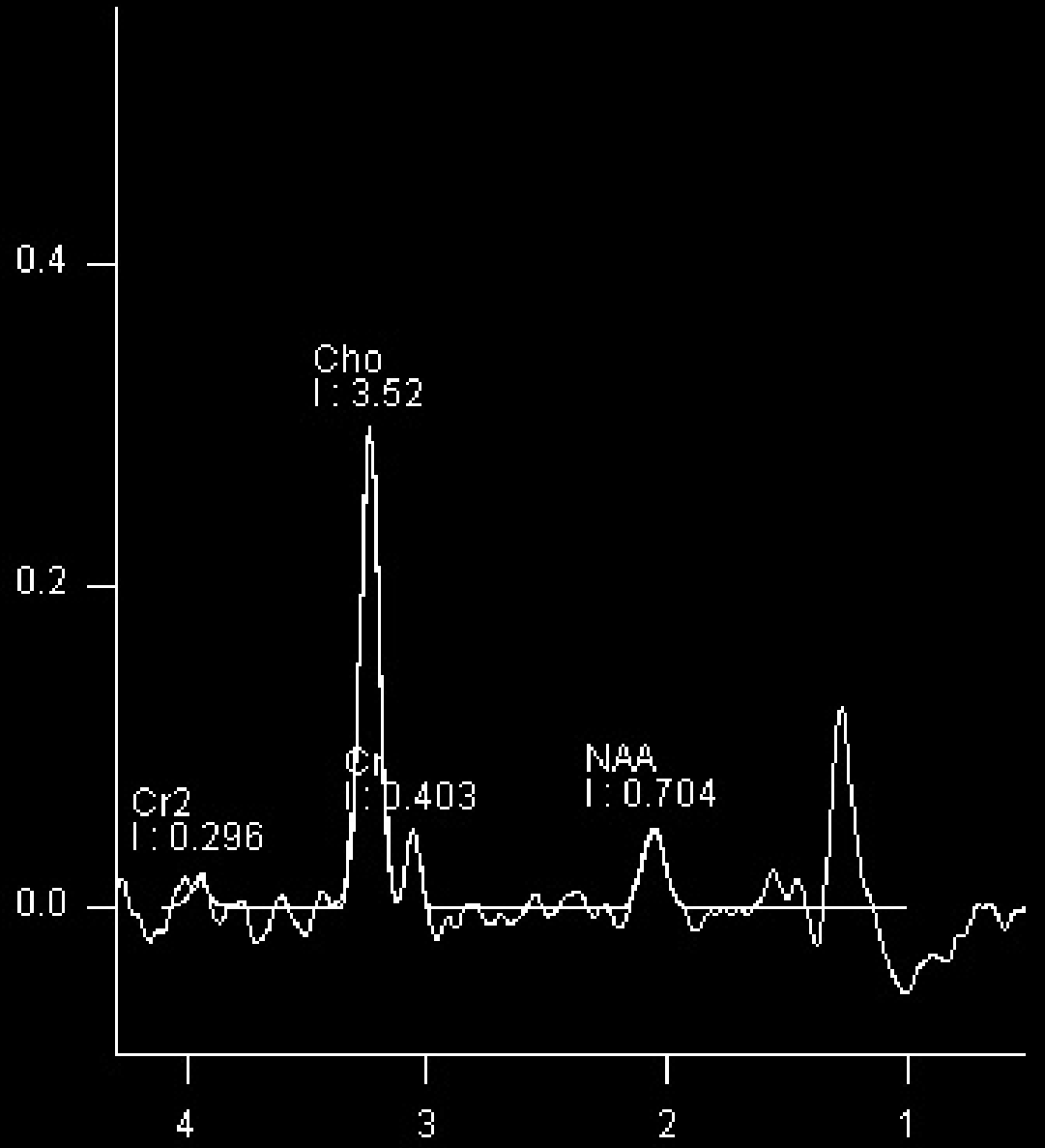


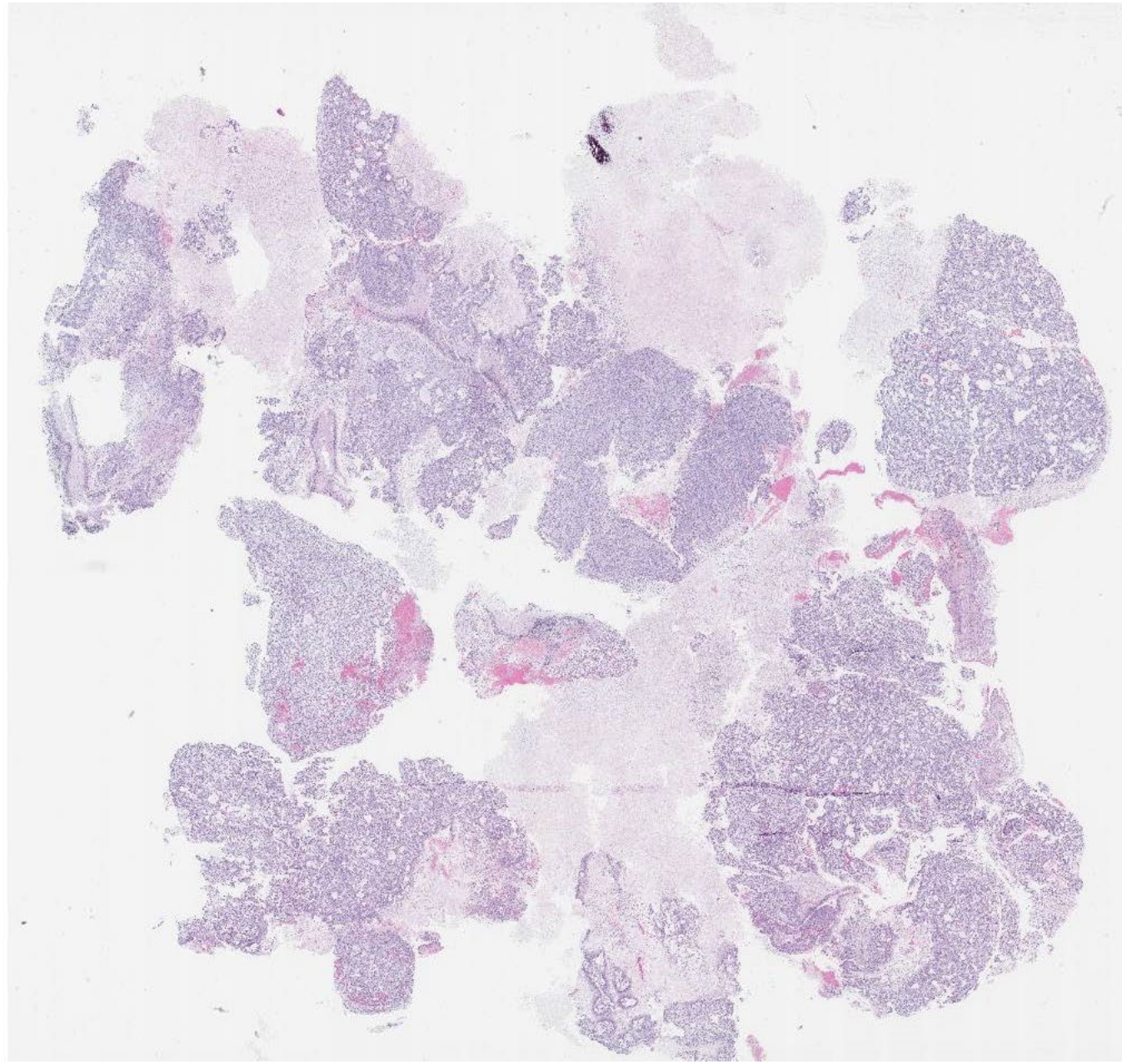


Poor Contrast Uptake



High-Grade MRS





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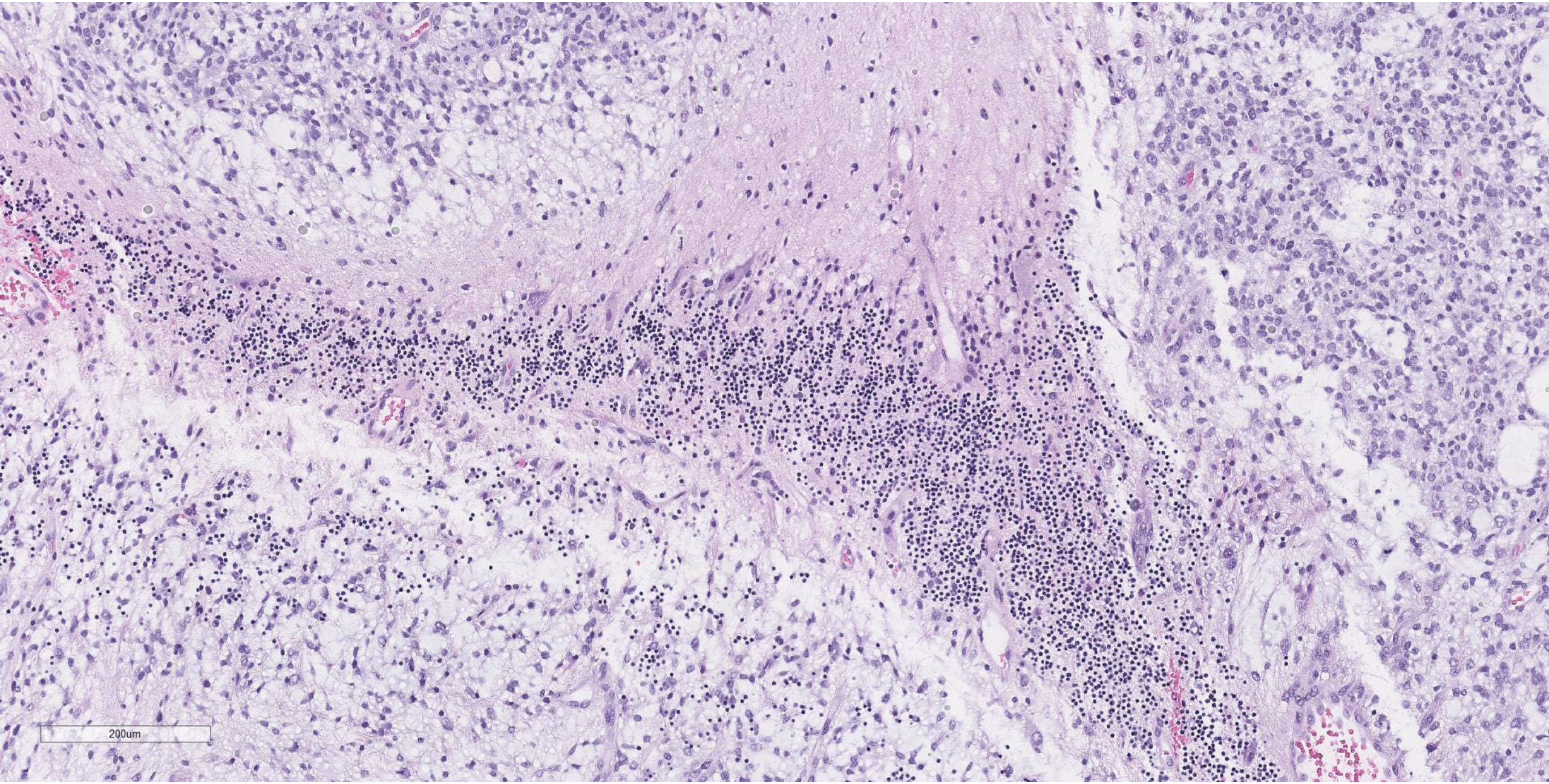
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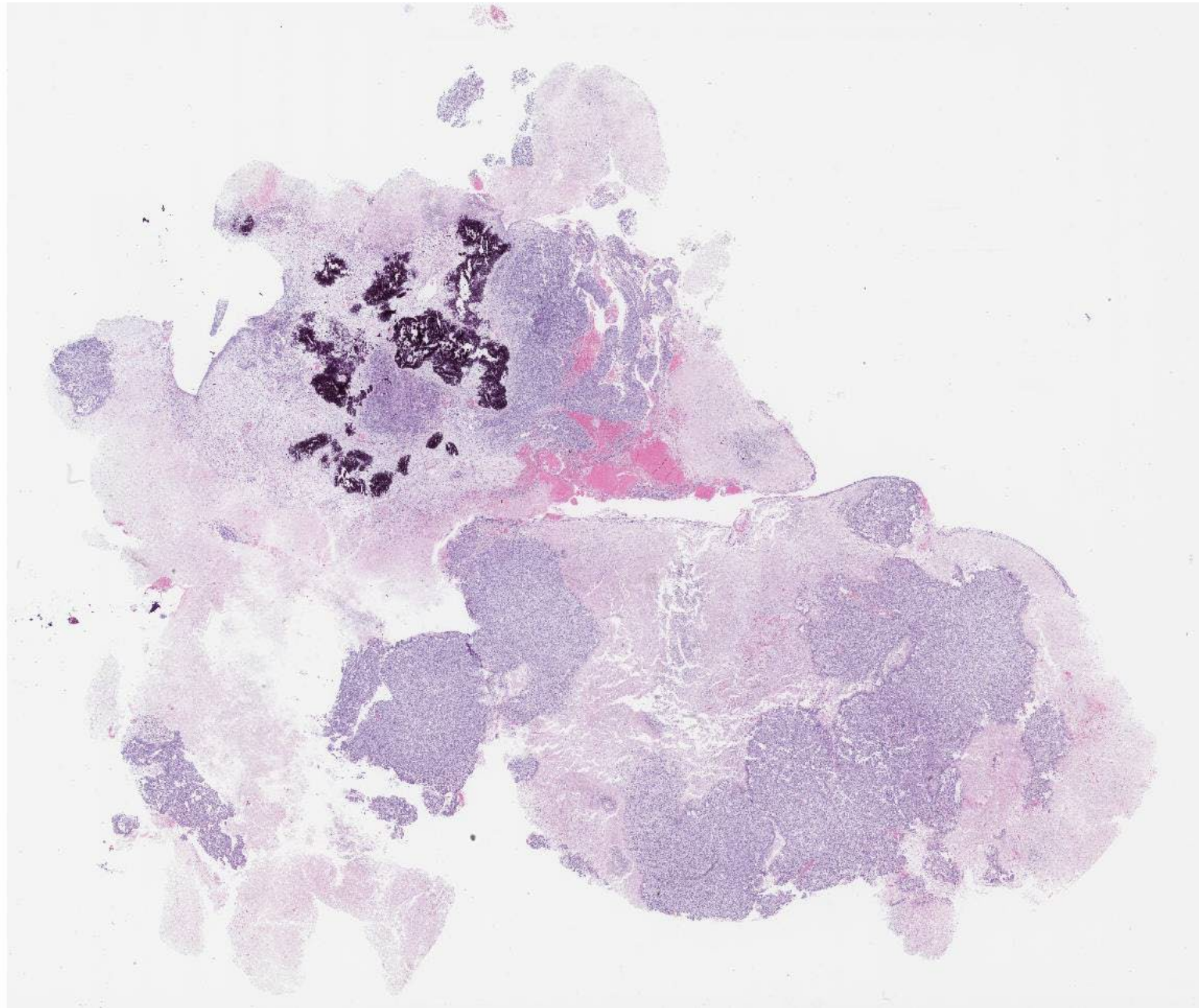

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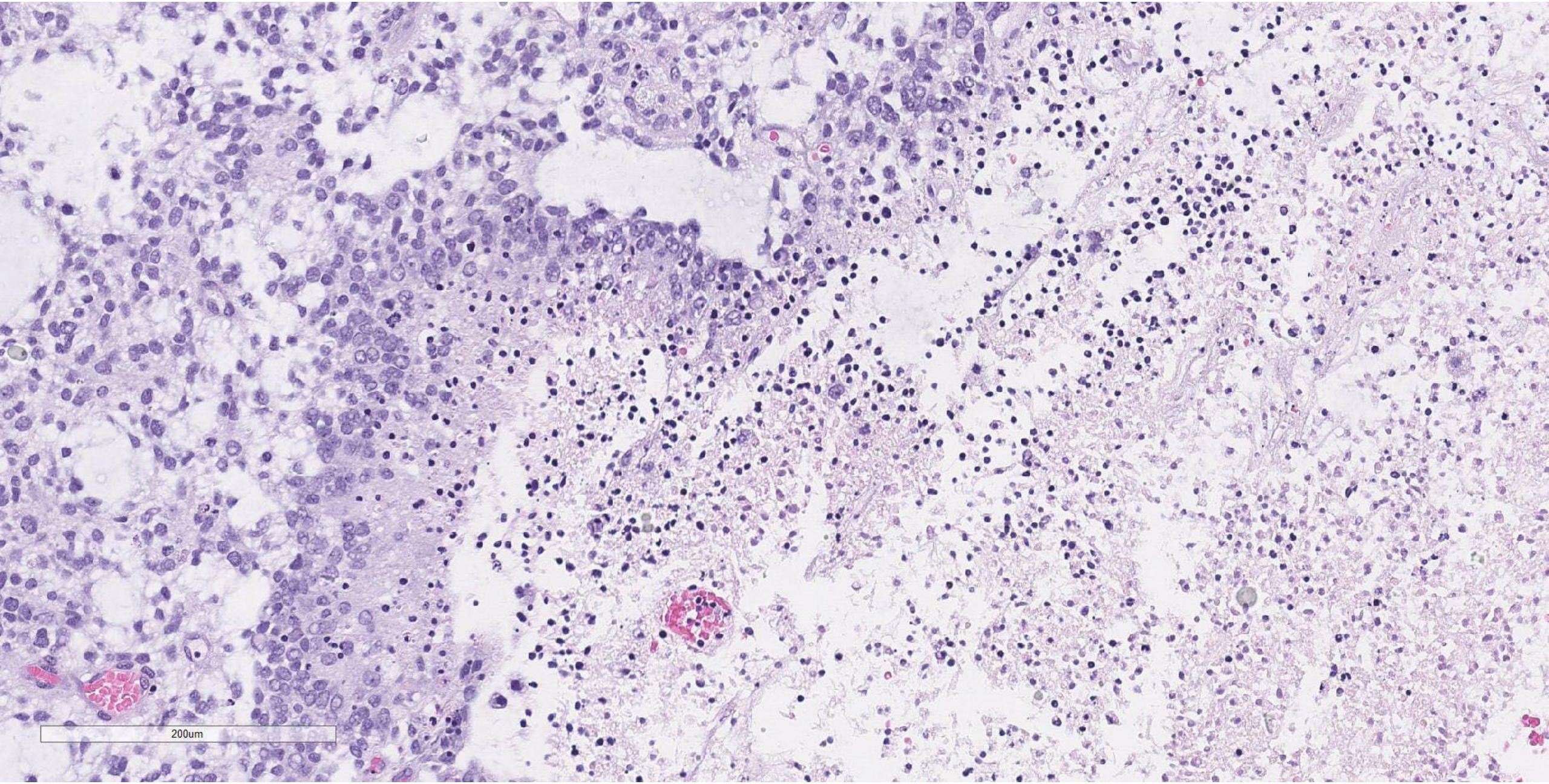
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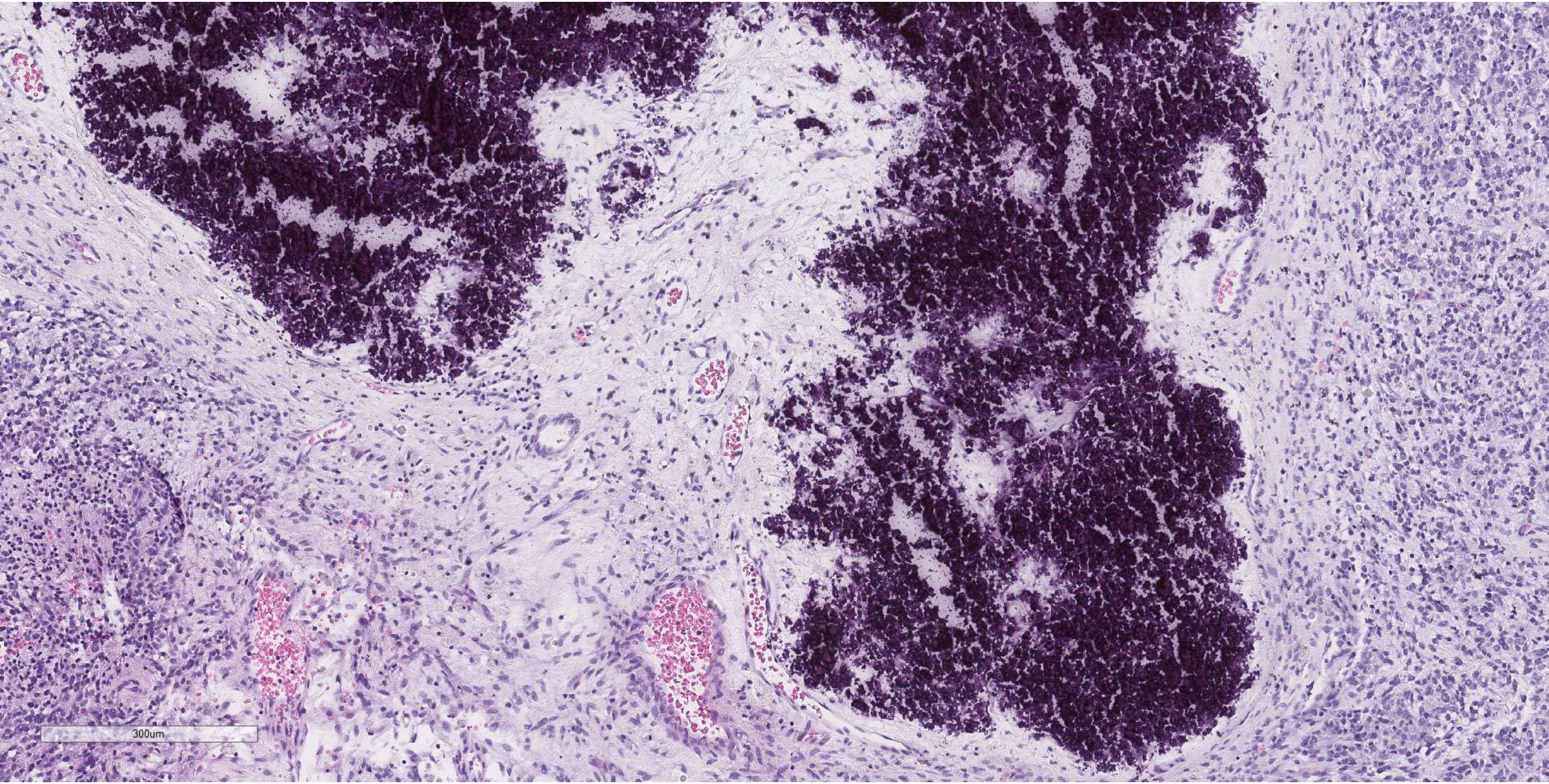
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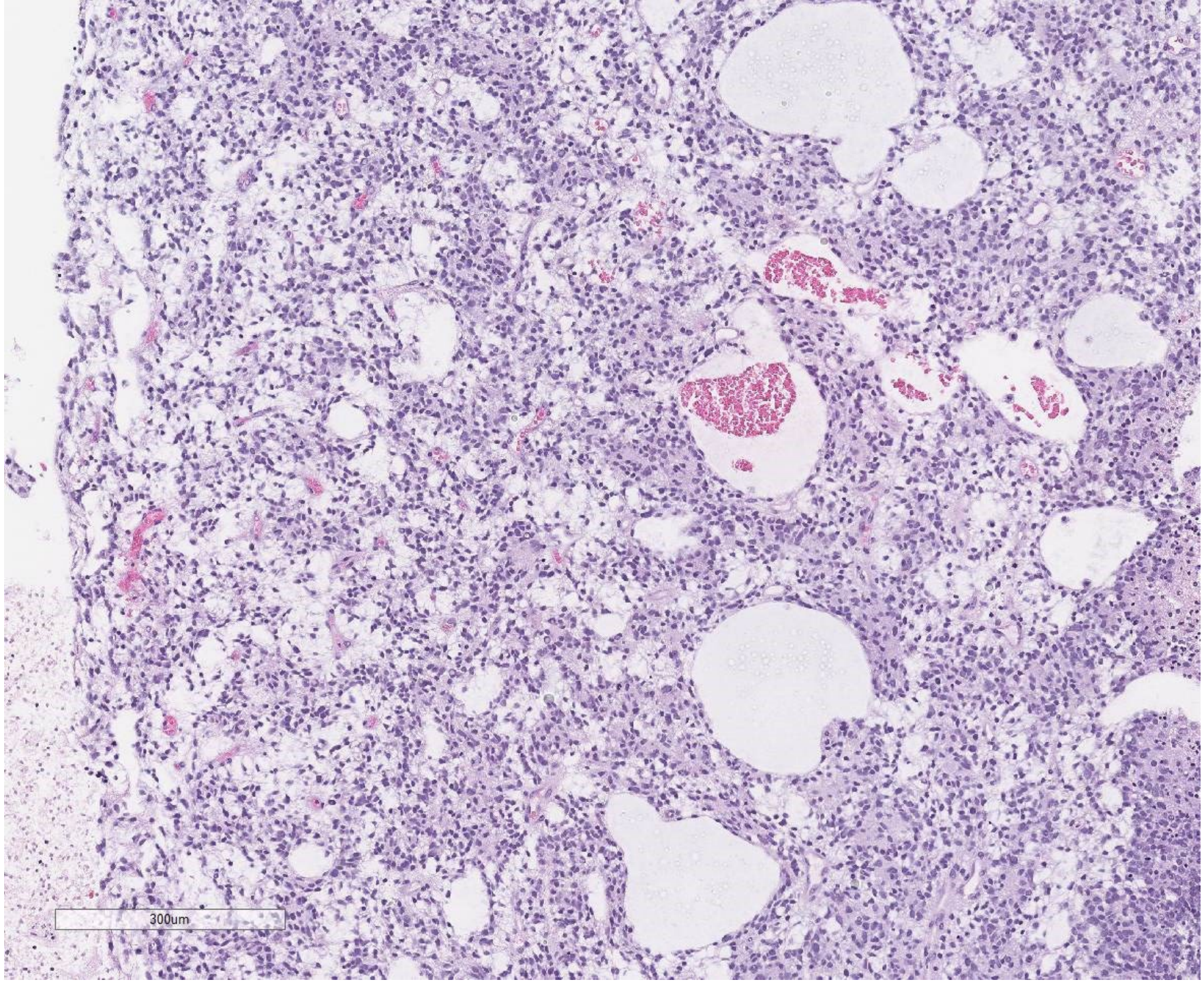
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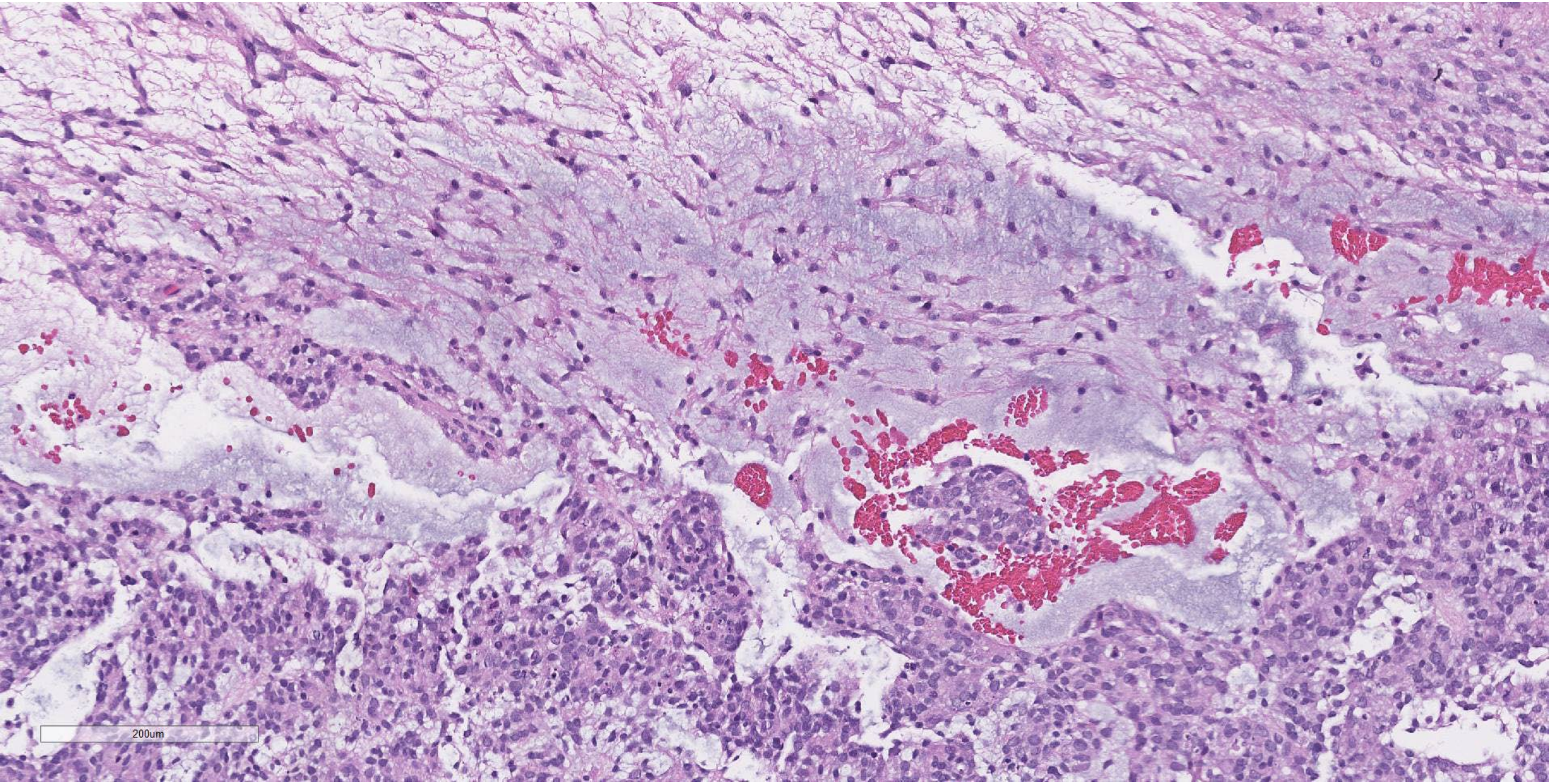
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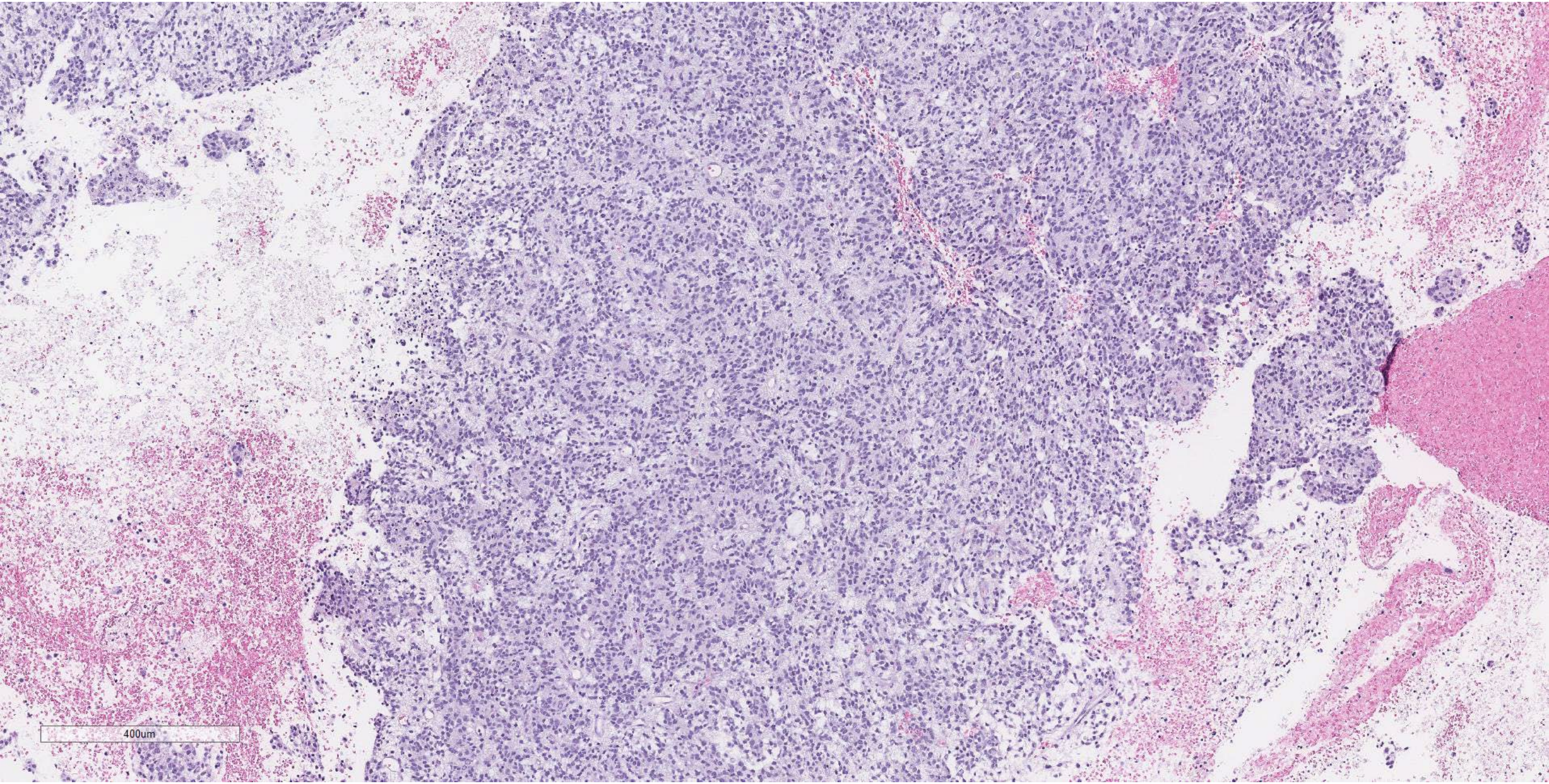
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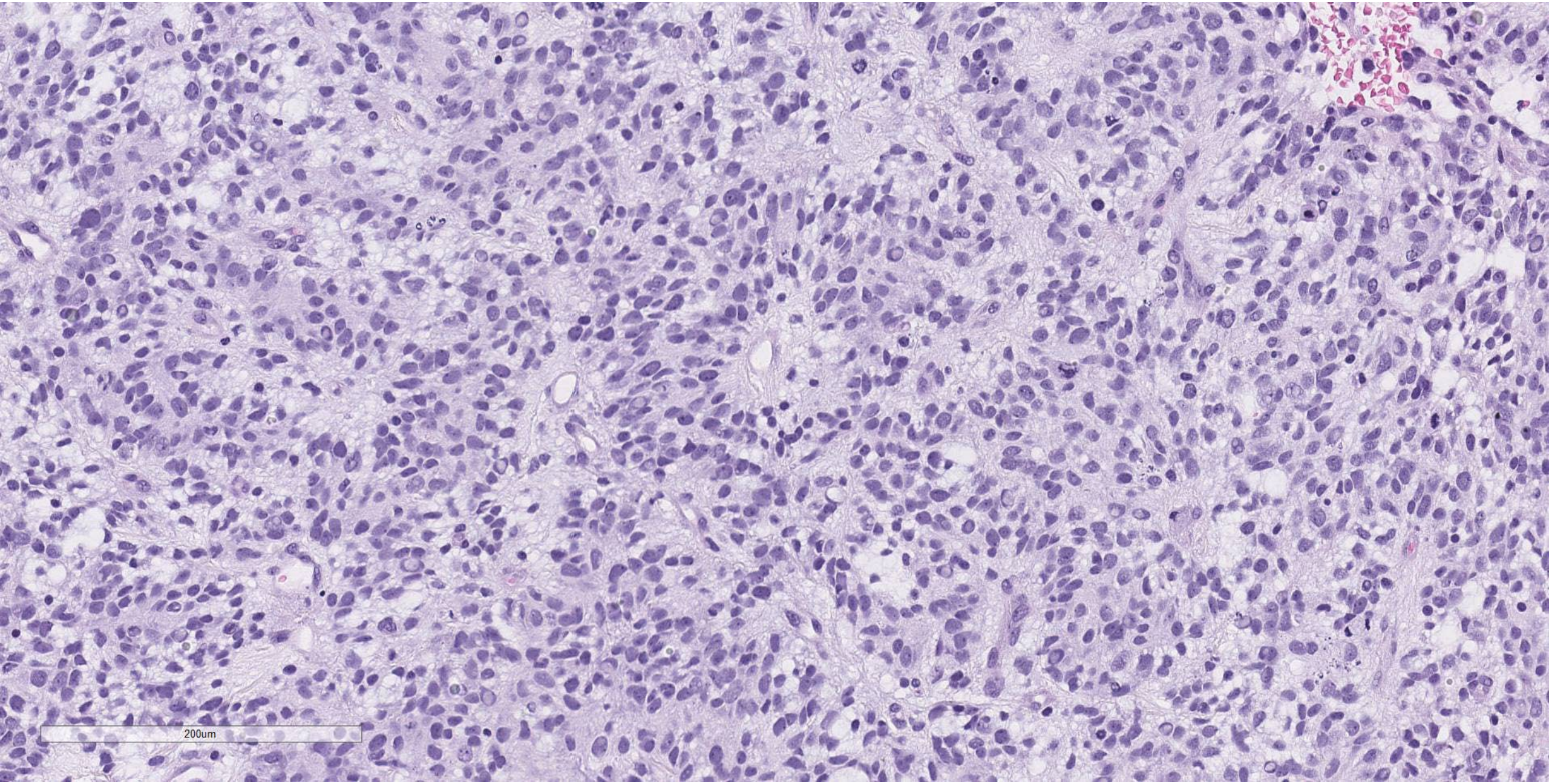
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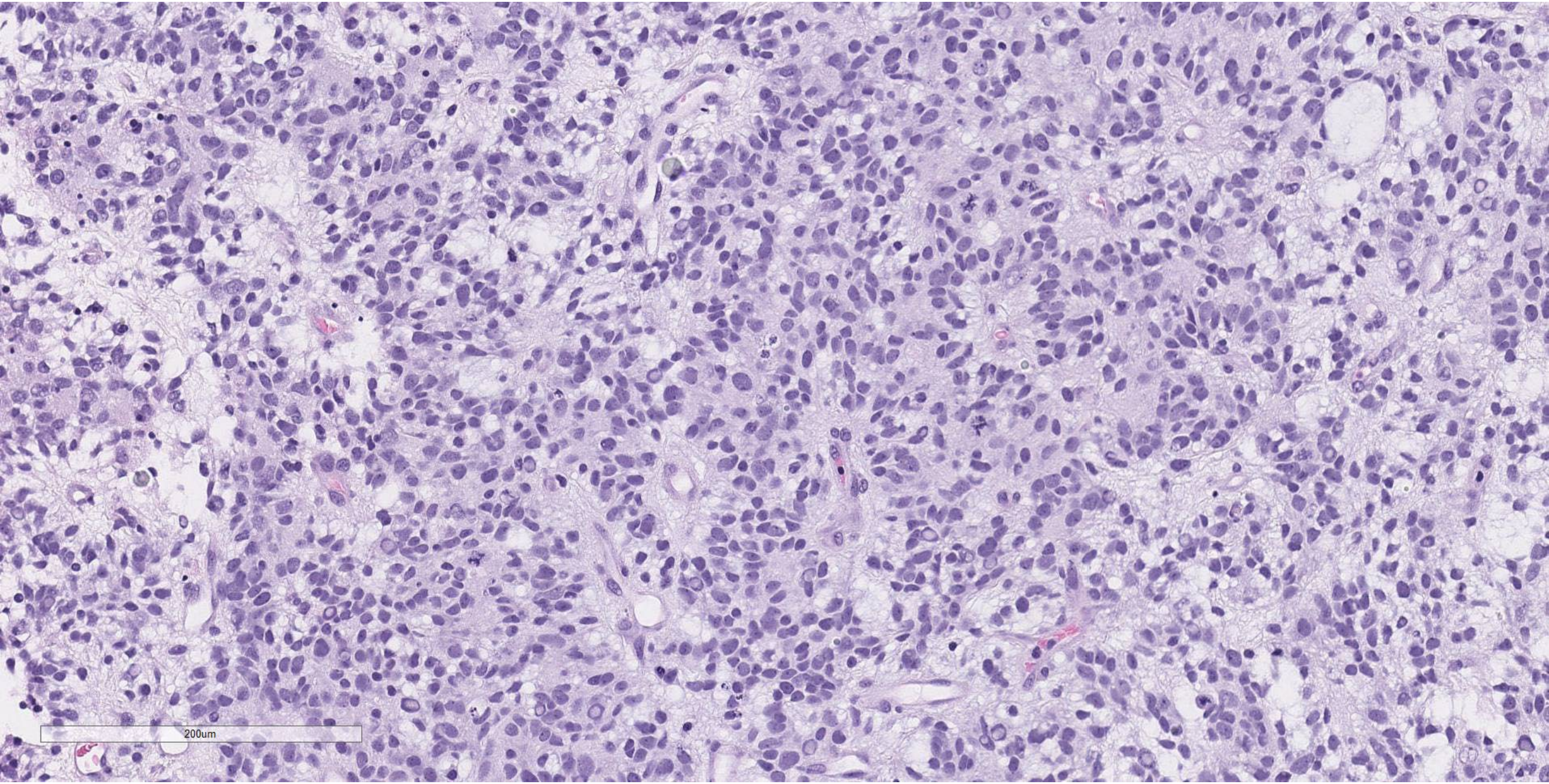
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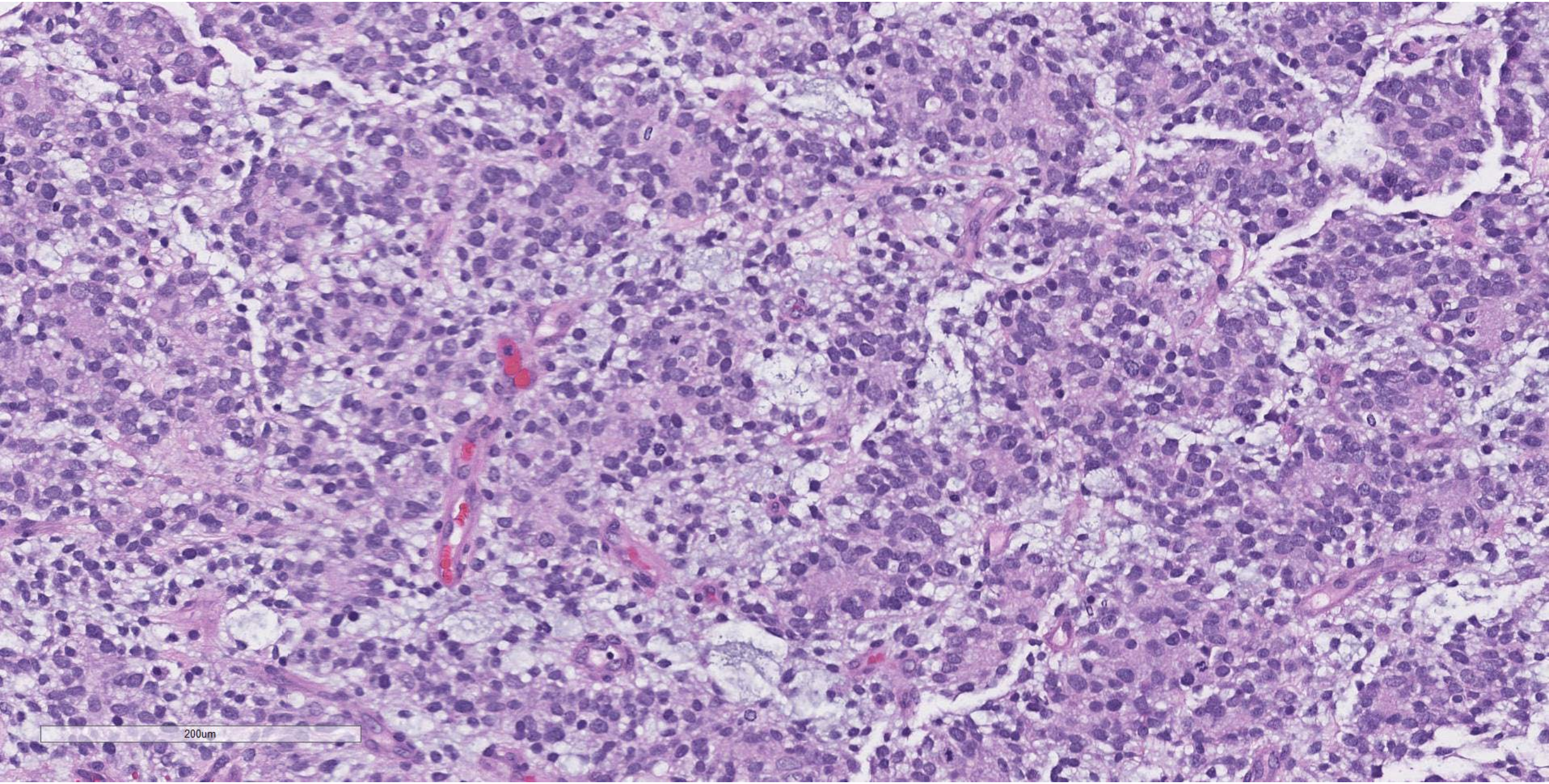
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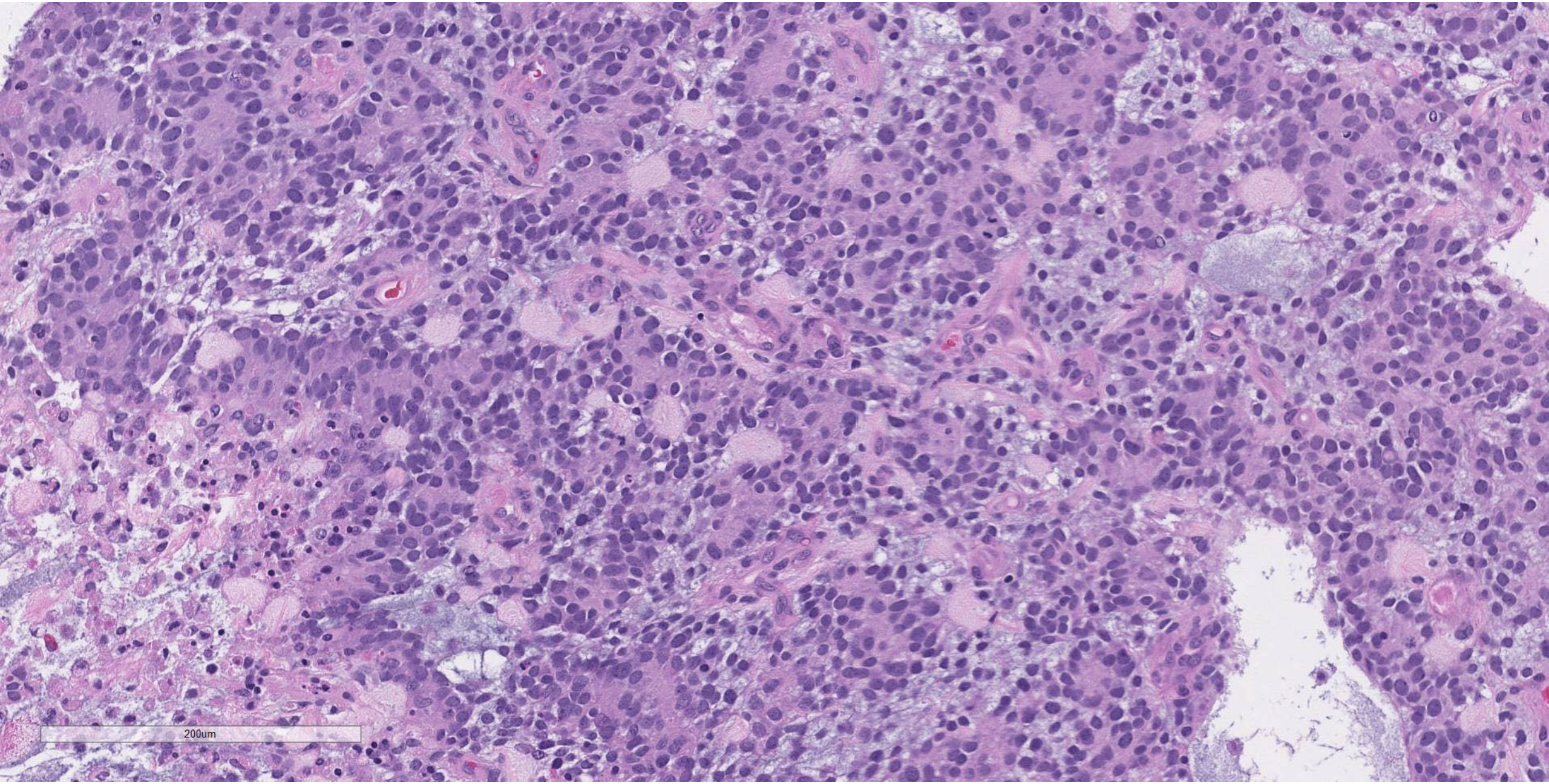
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Differential Diagnosis?

Published December 9, 2021 as 10.3174/ajnr.A7367

ORIGINAL RESEARCH
PEDIATRICS

Imaging Features with Histopathologic Correlation of CNS High-Grade Neuroepithelial Tumors with a *BCOR* Internal Tandem Duplication

L. Cardoen, A. Tauziède-Espariat, V. Dangouloff-Ros, S. Moalla, N. Nicolas, C.-J. Roux, Y. Bouchoucha, F. Bourdeaut, K. Beccaria, S. Bolle, G. Pierron, C. Dufour, F. Doz, N. Boddaert, and H.J. Brisse

ABSTRACT

BACKGROUND AND PURPOSE: A new brain tumor entity occurring in early childhood characterized by a somatic *BCL6* corepressor gene internal tandem duplication was recently described. The aim of this study was to describe the radiologic pattern of these tumors and correlate this pattern with histopathologic findings.

MATERIALS AND METHODS: This retrospective, noninterventional study included 10 children diagnosed with a CNS tumor, either by ribonucleic acid–sequencing analysis or deoxyribonucleic acid methylation analysis. Clinical, radiologic, and histopathologic data were collected. A neuropathologist reviewed 9 tumor samples. Preoperative images were analyzed in consensus by 7 pediatric radiologists.

RESULTS: All tumors were relatively large (range, 4.7–9.2 cm) intra-axial peripheral masses with well-defined borders and no peritumoral edema. All tumors showed mild and heterogeneous enhancement and marked restriction on DWI of the solid portions. Perfusion imaging showed a relatively lower CBF in the tumor than in the adjacent normal parenchyma. Nine of 10 tumors showed areas of necrosis, with the presence of hemorrhage in 8/10 and calcifications in 4/7. Large intratumoral macroscopic veins were observed in 9/10 patients. No intracranial or spinal leptomeningeal dissemination was noted at diagnosis.

CONCLUSIONS: CNS tumors with a *BCL6* corepressor gene internal tandem duplication present as large intra-axial peripheral masses with well-defined borders, no edema, restricted diffusion, weak contrast enhancement, frequent central necrosis, hemorrhage and calcifications, intratumoral veins, and no leptomeningeal dissemination at the time of diagnosis. Knowledge of these imaging characteristics may aid in histologic, genomic, and molecular profiling of brain tumors in young children.

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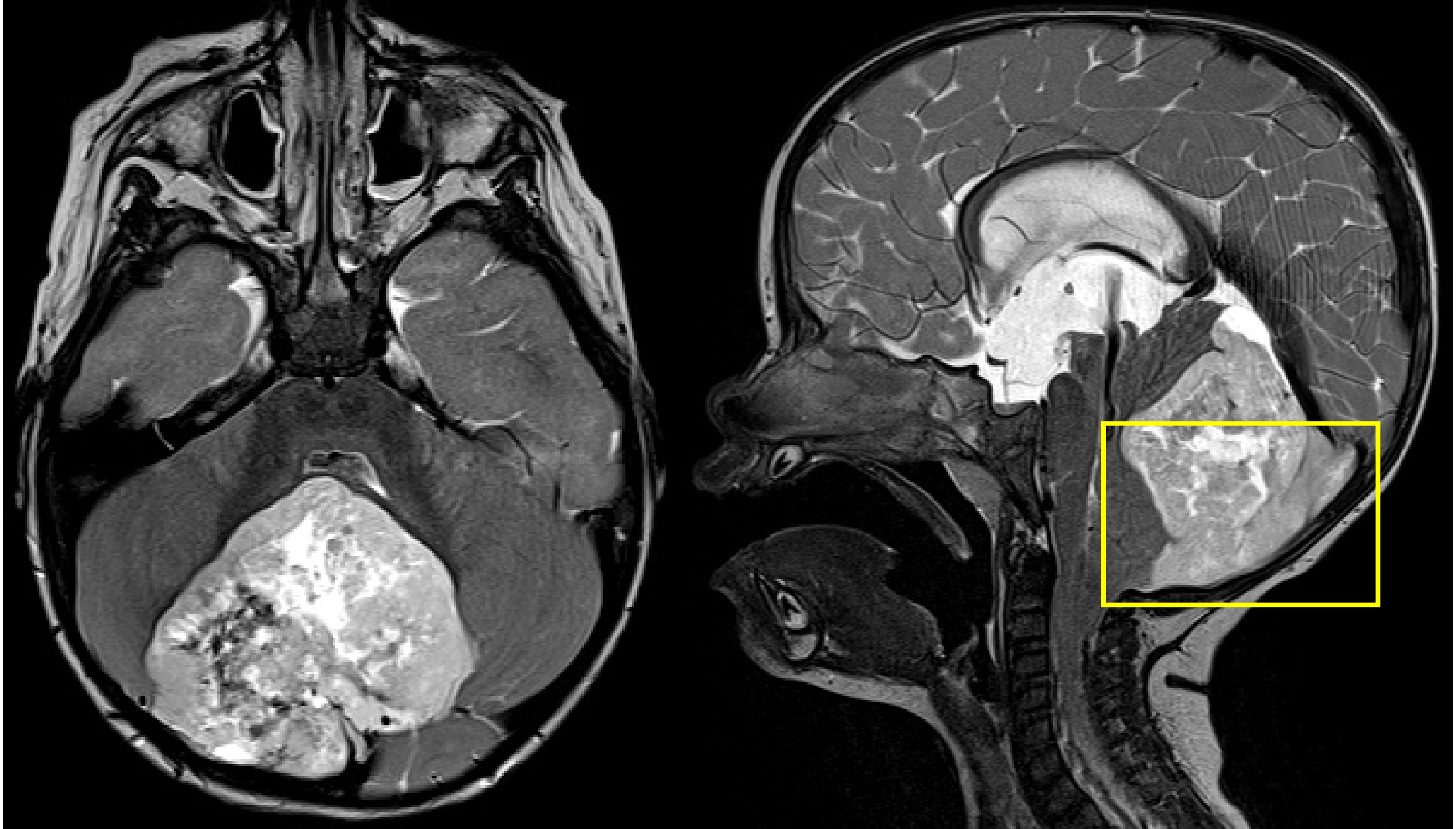


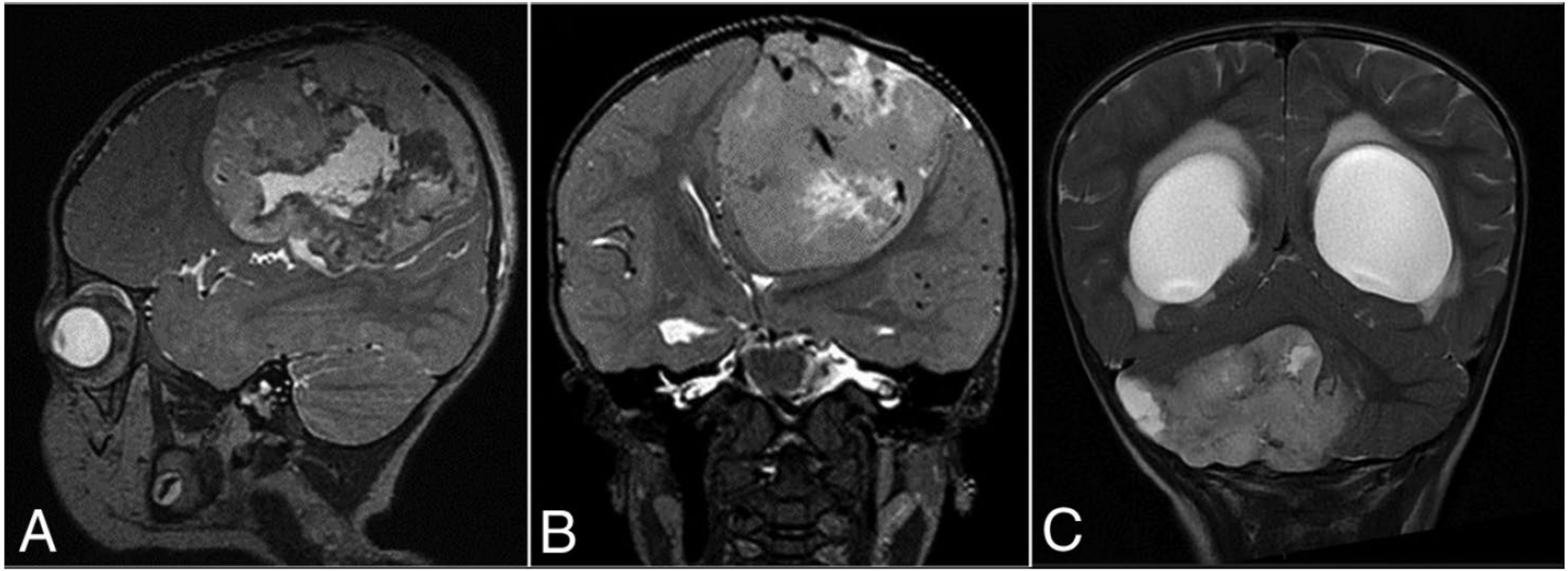


FIG 1. T2-weighted MR images showing large masses located supratentorially (*A* and *B*) and infratentorially (*C*).

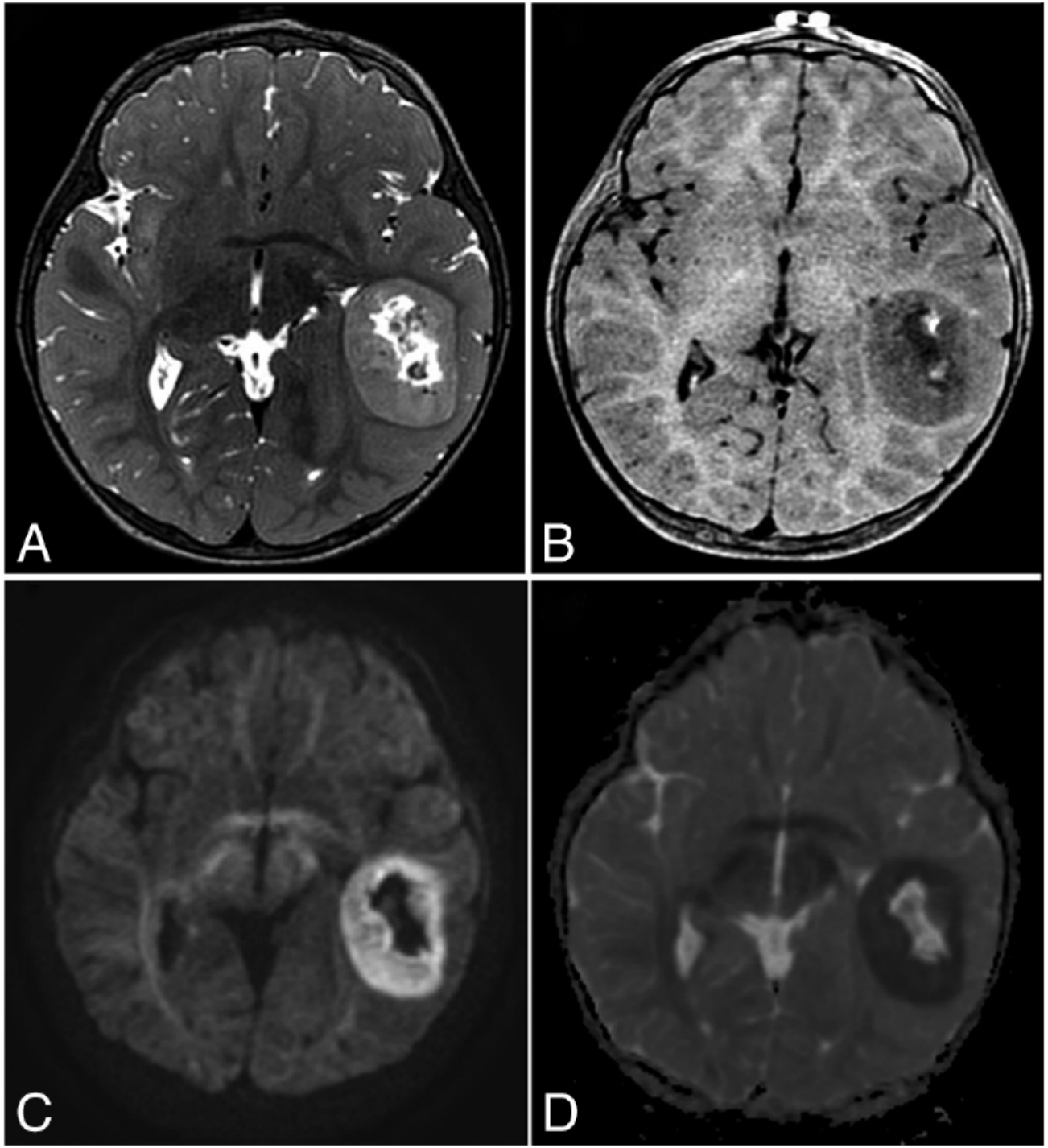


FIG 2. Characteristic MR imaging features of CNS tumors with a *BCOR* ITD. *A*, Axial T2-weighted image shows a well-defined mass, central necrosis, and no surrounding edema. *B*, Axial contrast-enhanced T1-weighted image shows poor enhancement after contrast medium administration. Axial DWI (*C*) and ADC map (*D*) show restricted diffusion of the solid portions of the tumor.

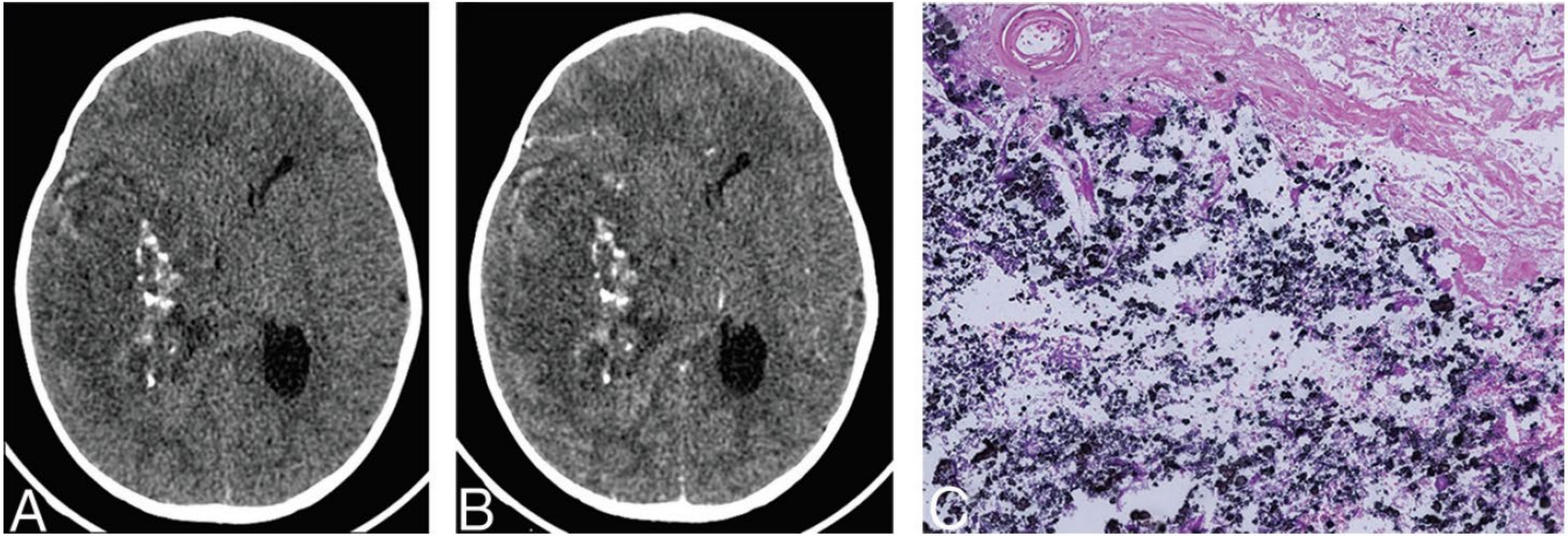


FIG 3. Axial CT images before (*A*) and after (*B*) contrast medium administration. The tumor is hypo to isodense relative to the cortex, and it exhibits weak-to-mild contrast enhancement. Intralesional calcifications are well-visualized. *C*, Visualization of several calcifications (*black stained*) (hematoxylin phloxine saffron, original magnification ×100).

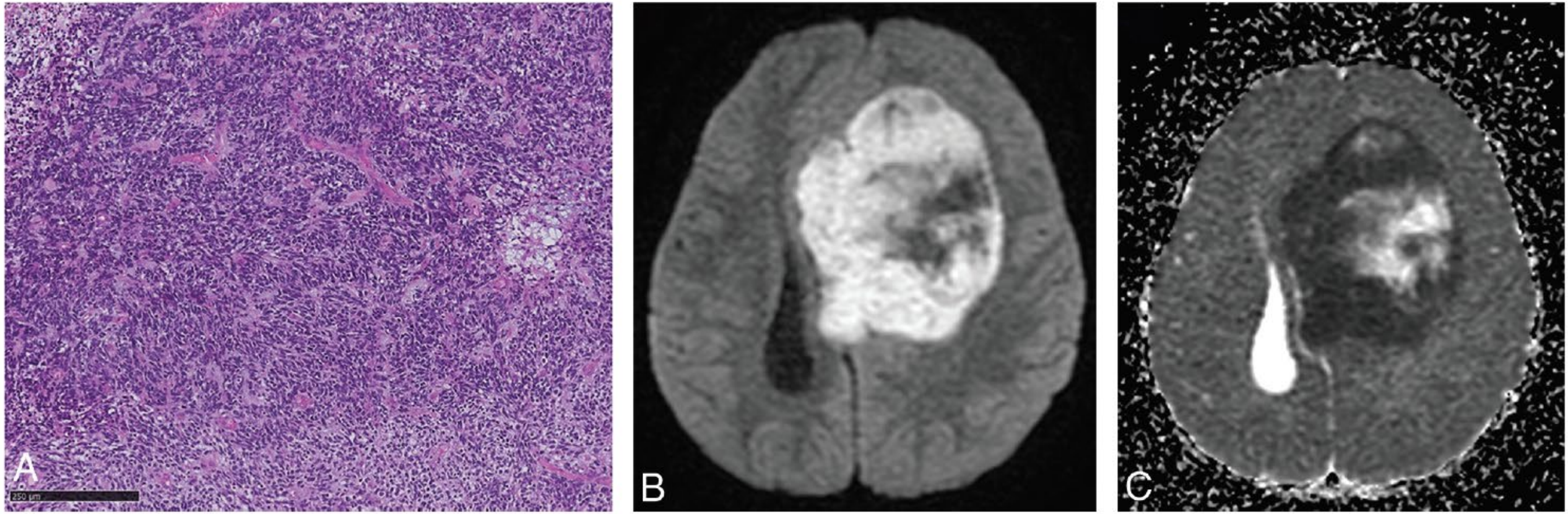
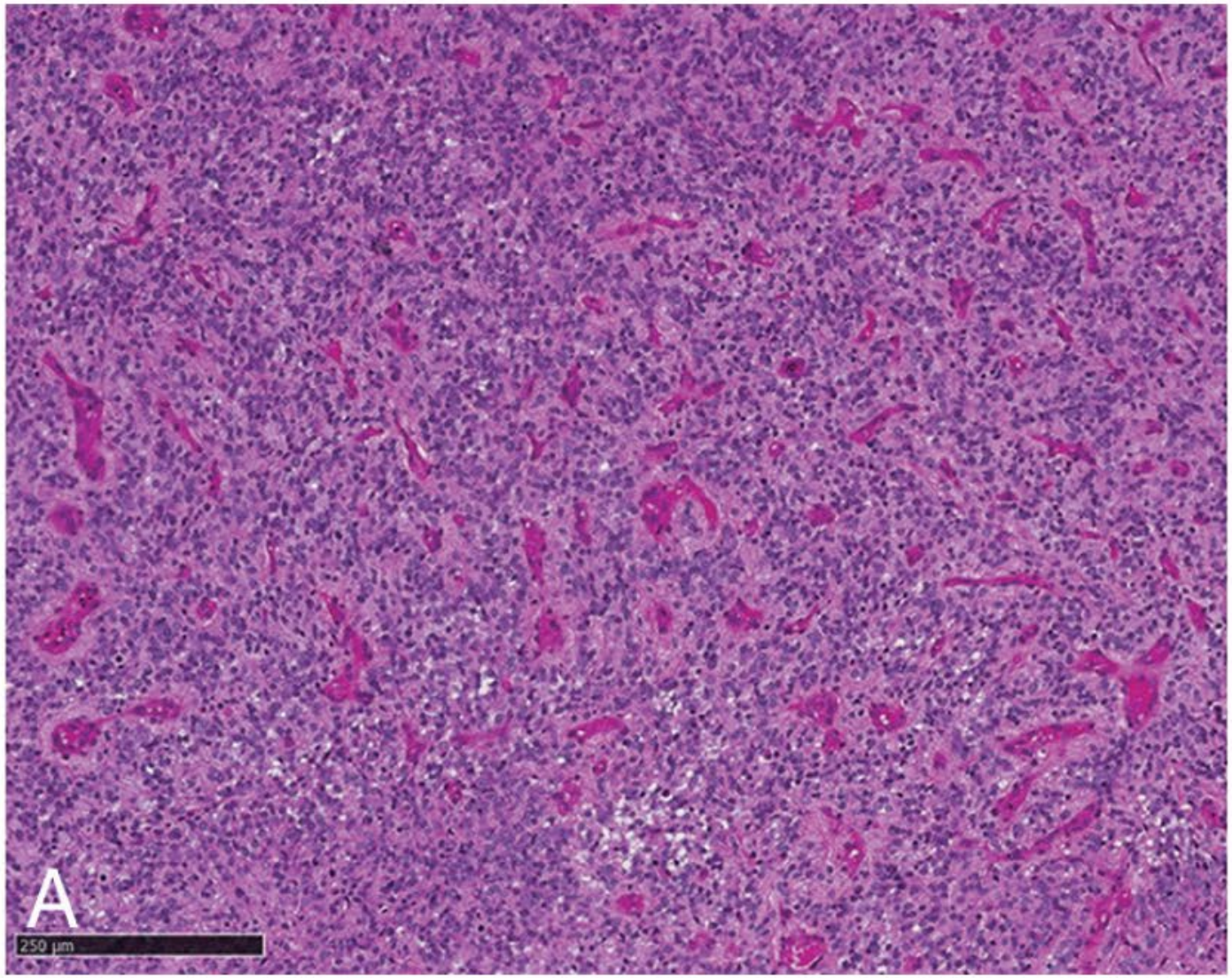


FIG 4. *A*, High cellular density of the tumor with numerous nuclei, densely packed (hematoxylin phloxine saffron, original magnification ×100). *Black scale bar* represents 250 µm. Note the corresponding diffusion-weighted image (*B*) with ADC mapping (C).



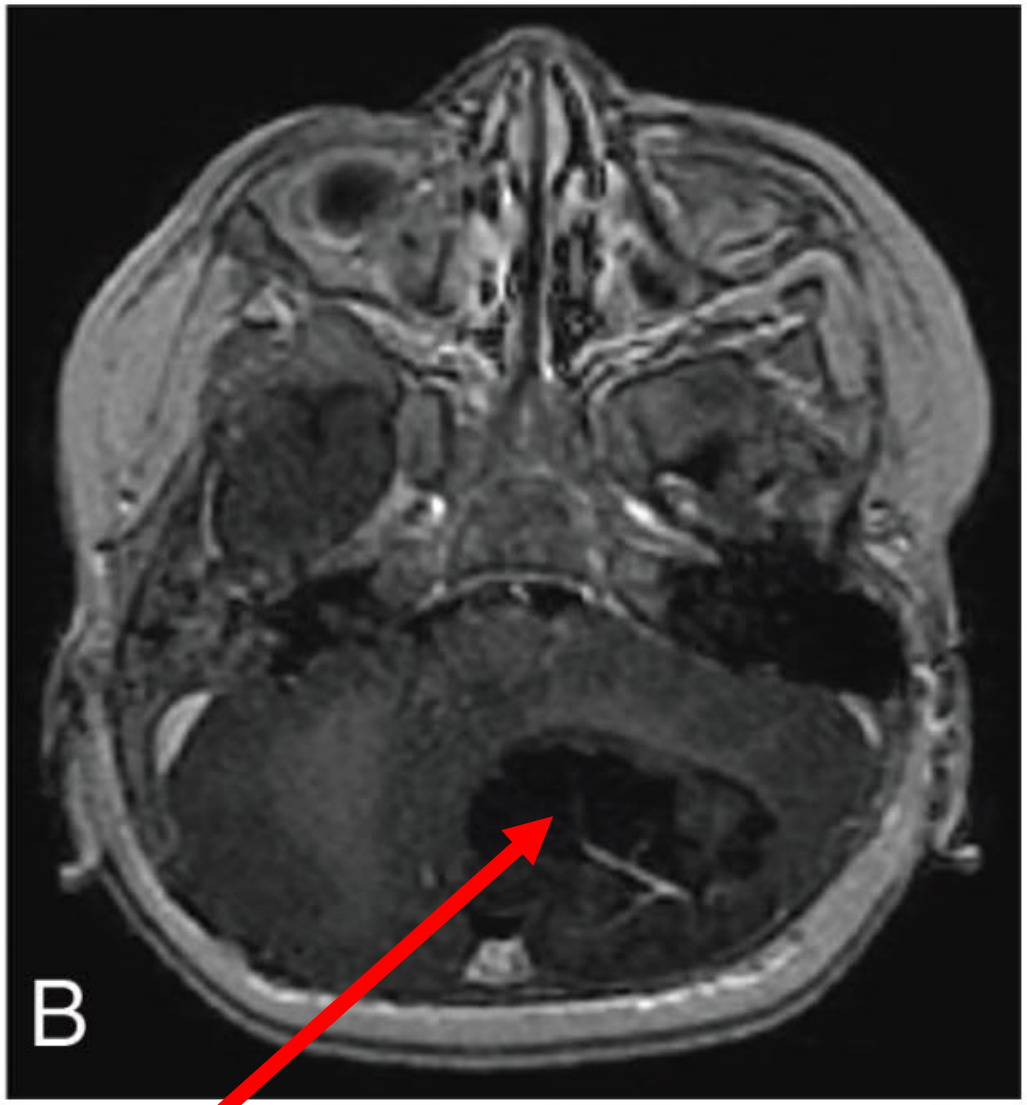


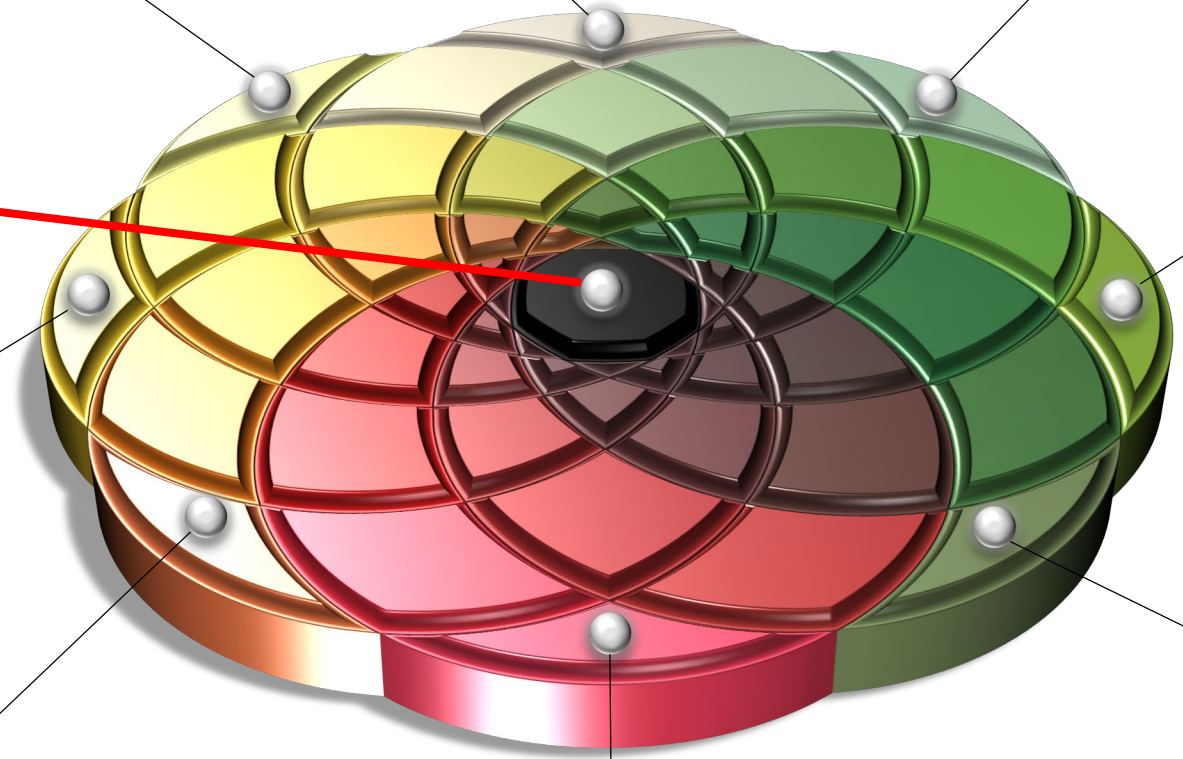
FIG 5. *A*, Rich delicate thin-walled vessels without microvascular proliferation (hematoxylin phloxine saffron, original magnification ×100). *Black scale bar* represents 250 µm. *B*, Corresponding contrast-enhanced T1-weighted MR image shows weak contrast uptake.

8 Data Spheres

Integrated Oncologic Diagnosis

- Age
- Gender
- History
- Anatomic Location (including Neurosurgeon's intraoperative observations)
- Imaging Characteristics (CT, MRI, PET-CT, MRS, Perfusion Metrics)
- Histologic Features (Cytologic Prep, Frozen Section, FFPE)
- Differentiation Markers (IHC)
- Molecular Signature (IHC / FISH / PCR / NGS / DNA Methylation Profiling)

8 Data Sphere Model for Oncologic Diagnosis



Age

Molecular Signature

Gender

Diagnosis

Clinical History

Differentiation Markers

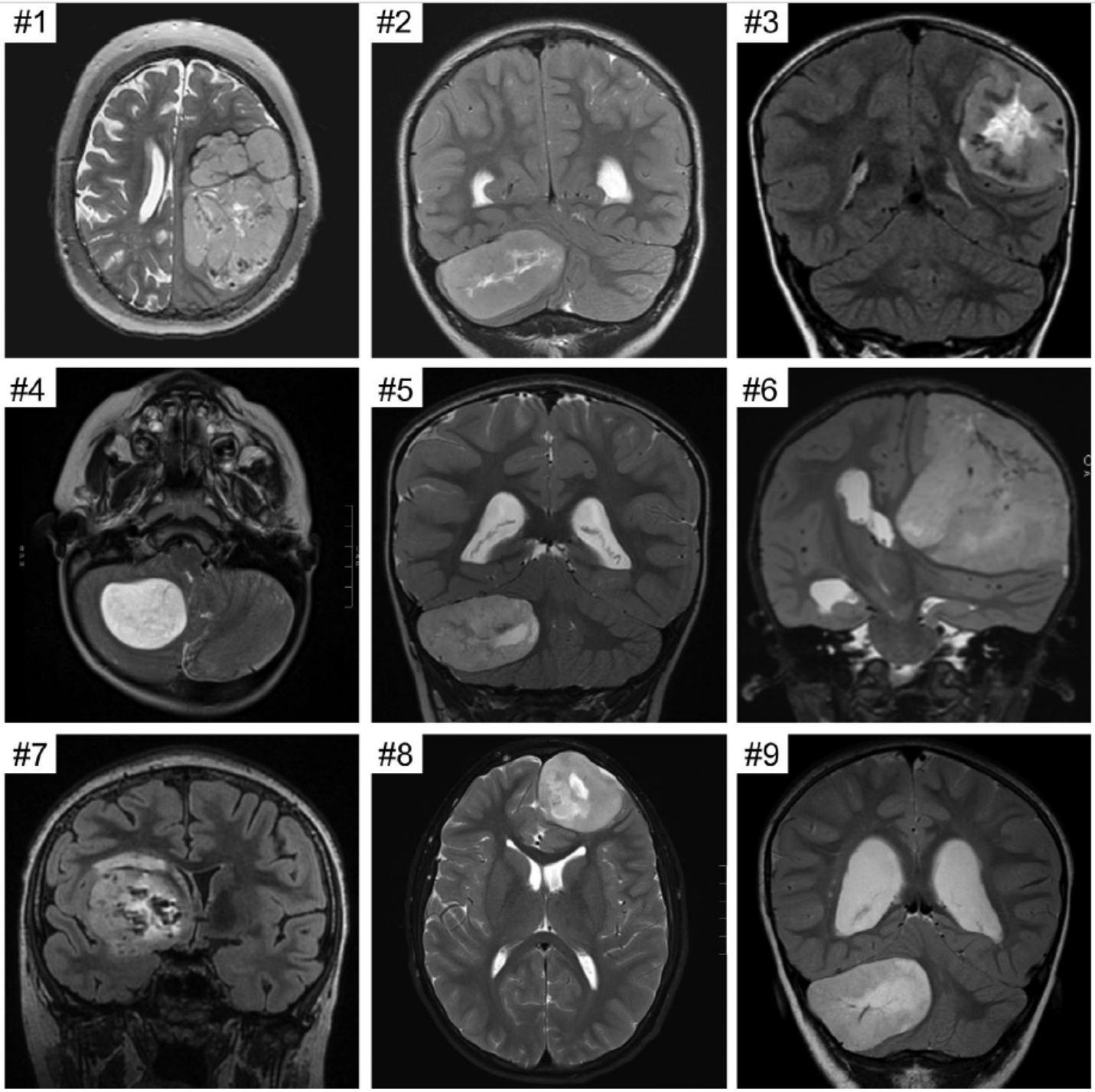
Morphology

Anatomic Location

Imaging Characteristics

High-grade neuroepithelial tumor with *BCOR* exon 15 internal tandem duplication—a comprehensive clinical, radiographic, pathologic, and genomic analysis

Sean P. Ferris[1]; Jose Velazquez Vega[2]; Mariam Aboian[3]; Julieann C. Lee[1]; Jessica Van Ziffle[1,4]; Courtney Onodera[1,4]; James P. Grenert[1,4]; Tara Saunders[1]; Yunn-Yi Chen[1]; Anu Banerjee[5]; Cassie N. Kline[5,6]; Nalin Gupta[7]; Corey Raffel[7]; David Samuel[8]; Irune Ruiz-Diaz[9]; Shino Magaki[10]; Dianne Wilson[11]; Janna Neltner[11]; Zahra Al-Hajri[12]; Joanna J. Phillips[1,7]; Melike Pekmezci[1]; Andrew W. Bollen[1]; Tarik Tihan[1]; Matthew Schniederjan[2]; Soonmee Cha[3]; Arie Perry[1,7]; David A. Solomon[1,4,]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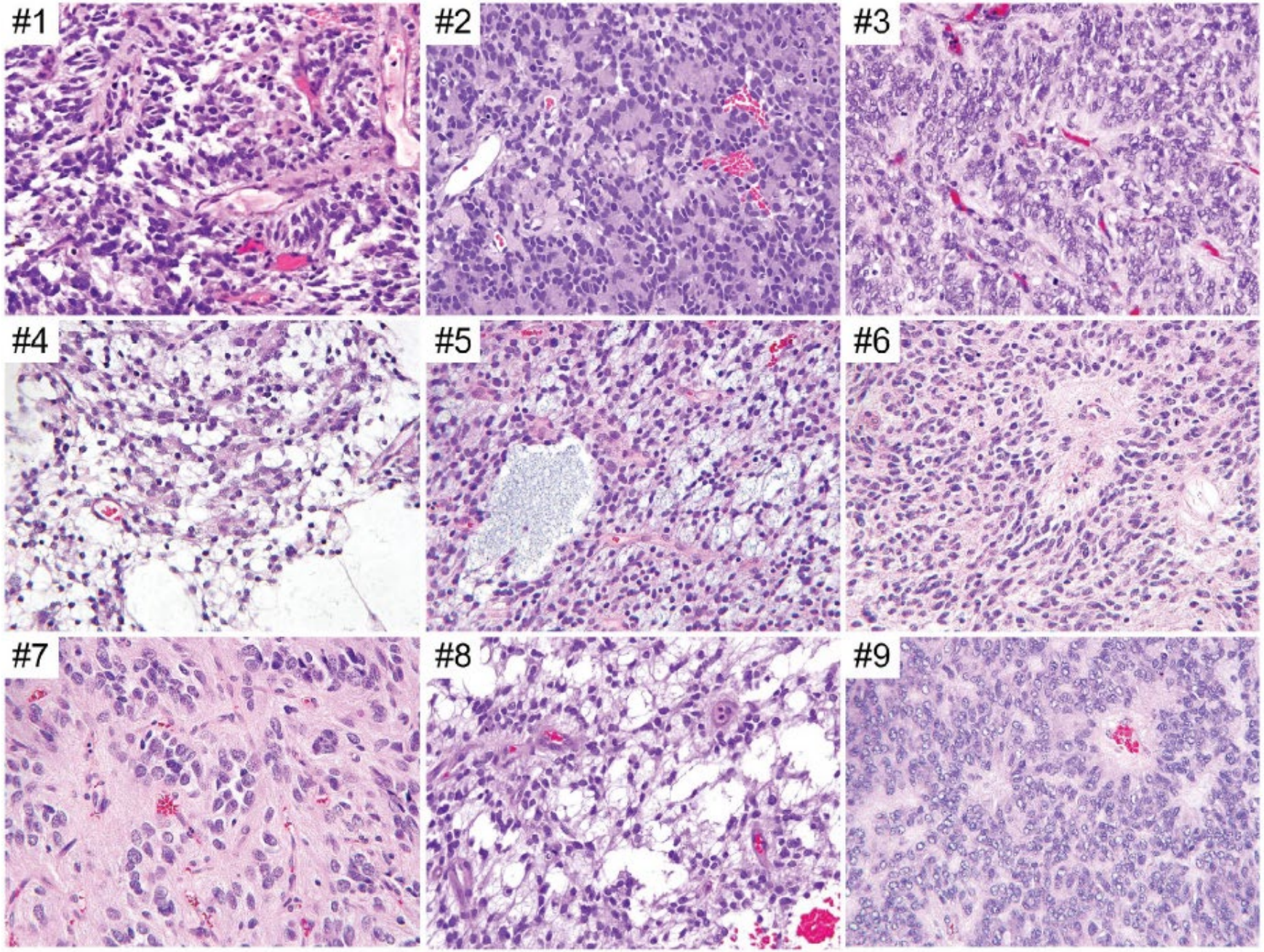
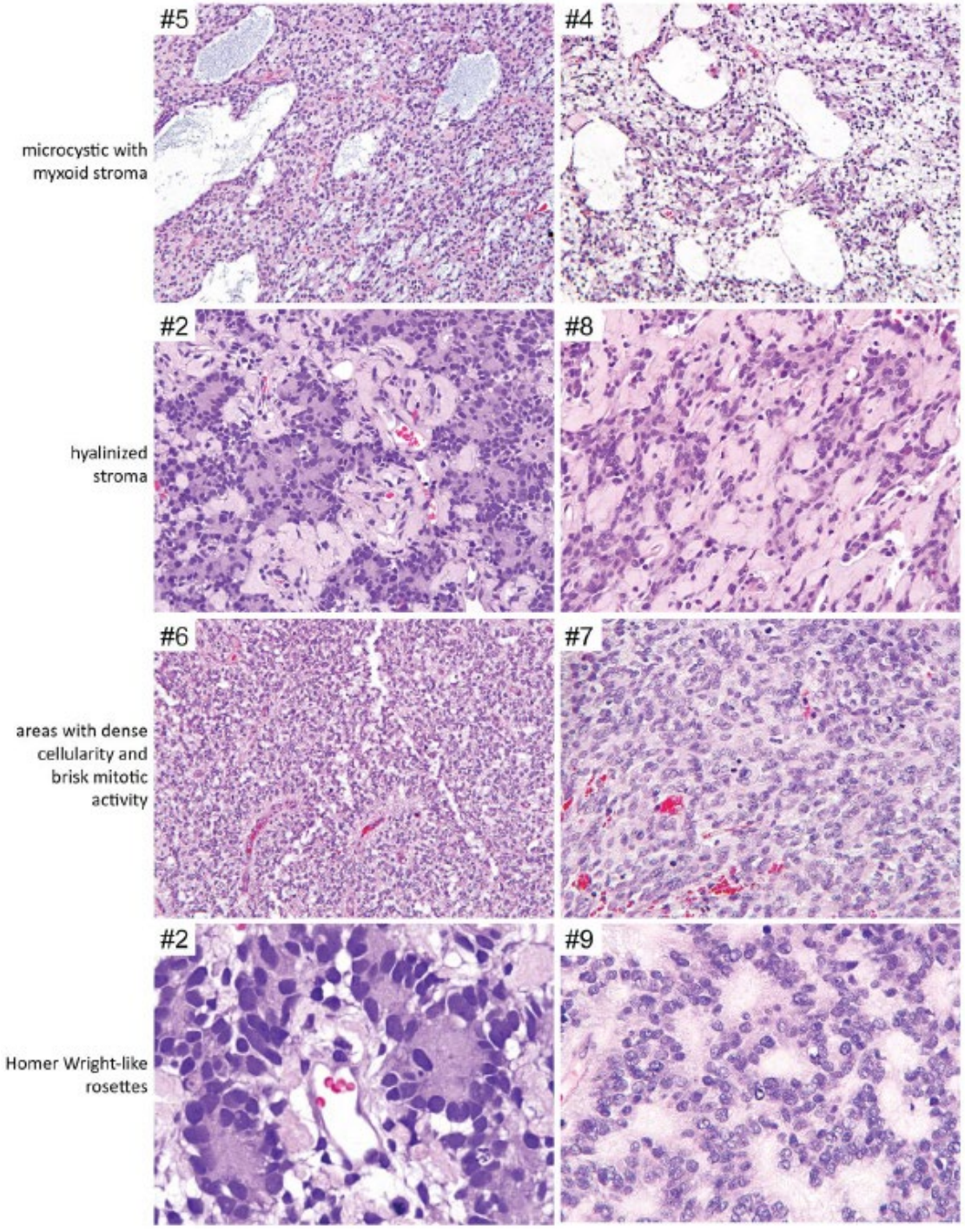
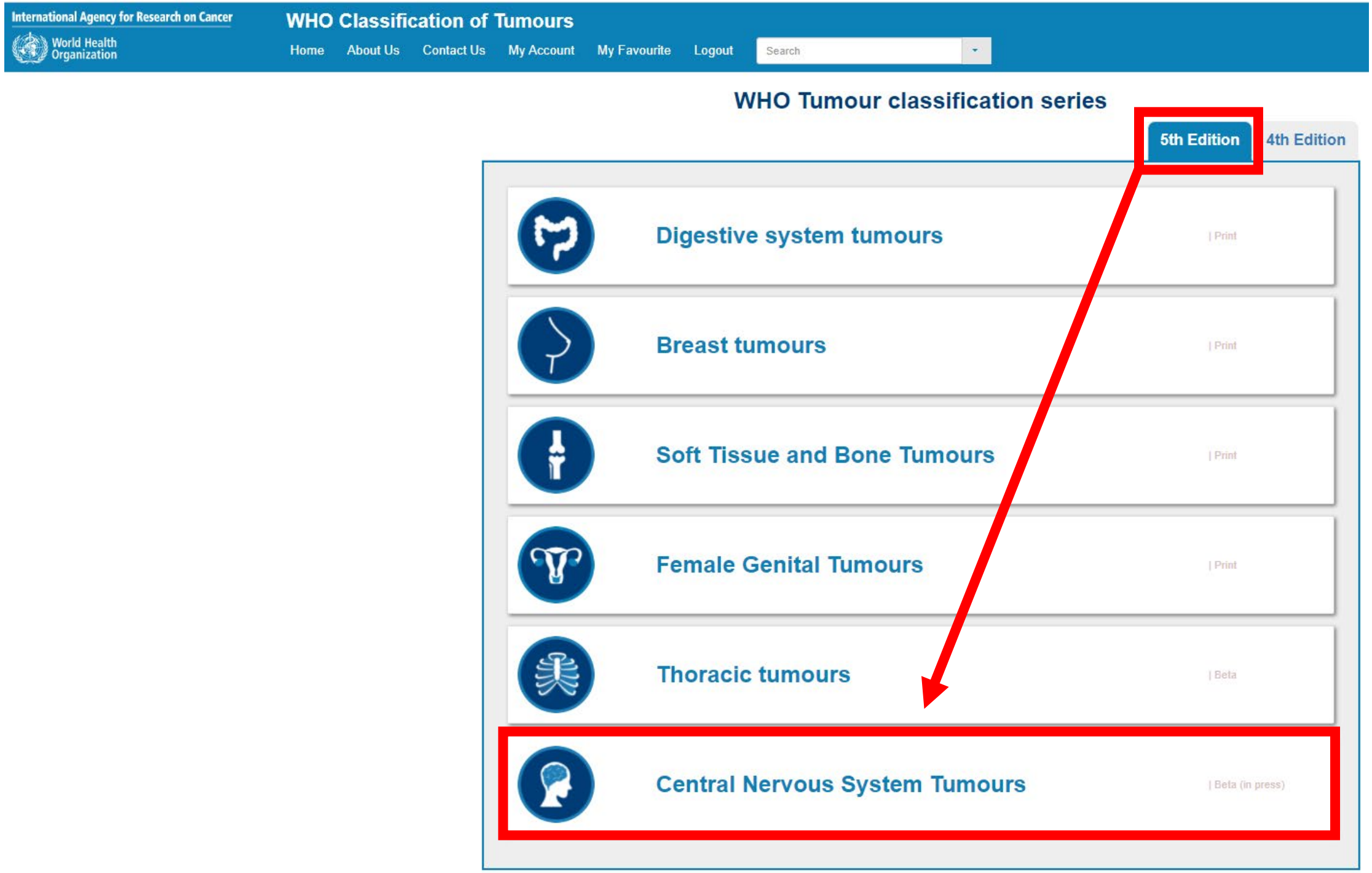


Figure 2. *Histologic features of the CNS high-grade neuroepithelial tumors with BCOR exon 15 internal tandem duplication.* Shown are representative hematoxylin and eosin (H&E)-stained sections of cases #1–9.

Figure 3. *Recurrent histologic features observed in CNS high-grade neuroepithelial tumor with BCOR exon 15 internal tandem duplication.* Shown are H&E-stained sections demonstrating the circumscribed growth, palisading necrosis, perivascular pseudorosettes, and glioma-like fibrillarity frequently observed in this tumor entity.

Figure 4. *Additional recurrent histologic features observed in a subset of CNS high-grade neuroepithelial tumor with BCOR exon 15 internal tandem duplication.* Shown are H&E-stained sections demonstrating the microcystic/myxoid background, hyalinized stroma, areas with dense cellularity and brisk mitotic activity, and Homer Wright-like rosettes observed in a subset of the cases.




International Agency for Research on Cancer
World Health Organization
WHO Classification of Tumours
Home
About Us
Contact Us
My Account
My Favourite
Logout
Search
WHO Tumour classification series
5th Edition
4th Edition
Digestive system tumours
| Print
Breast tumours
| Print
Soft Tissue and Bone Tumours
| Print
Female Genital Tumours
| Print
Thoracic tumours
| Beta
Central Nervous System Tumours
| Beta (in press)

3. Choroid plexus tumours

4. Embryonal tumours

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  - *Medulloblastomas, molecularly defined*
  - Medulloblastoma, WNT-activated
  - Medulloblastoma, SHH-activated and TP53-wildtype
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  - Medulloblastoma, histologically defined
- **Other CNS embryonal tumours**
  - Other CNS embryonal tumours: Introduction
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  - Cribriform neuroepithelial tumour
  - Embryonal tumour with multilayered rosettes
  - CNS neuroblastoma, FOXR2-activated
  - CNS tumour with BCOR internal tandem duplication
  - CNS embryonal tumour NEC/NOS

5. Pineal tumours

6. Cranial and paraspinal nerve tumours

7. Meningioma

8. Mesenchymal, non-meningothelial tumours involving the CNS

9. Melanocytic tumours

10. Haematolymphoid tumours involving the CNS

11. Germ cell tumours

12. Tumours of the sellar region

13. Metastases to the CNS

14. Genetic tumour syndromes involving the CNS

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- Medulloblastoma, SHH-activated and TP53-wildtype
- Medulloblastoma, SHH-activated and TP53-mutant
- Medulloblastoma, non-WNT/non-SHH

Medulloblastomas, histologically defined

- Medulloblastoma, histologically defined

Other CNS embryonal tumours

- Other CNS embryonal tumours: Introduction
- Atypical teratoid/rhabdoid tumour
- Cribriform neuroepithelial tumour
- Embryonal tumour with multilayered rosettes
- CNS neuroblastoma, FOXR2-activated
- CNS tumour with BCOR internal tandem duplication
- CNS embryonal tumour NEC/NOS

CNS tumour with BCOR internal tandem duplication

Definition

CNS tumour with *BCOR* internal tandem duplication (ITD) is a malignant CNS tumour characterized by a predominantly solid growth pattern, uniform oval or spindle-shaped cells with round to oval nuclei, a dense capillary network, focal pseudorosette formation, and an ITD in exon 15 of the *BCOR* gene.

Patient 5

Email from community hospital Neuro-Oncologist

Email from community hospital Neuro-Oncologist

“Would you mind having a look at the pathology slides for a patient of mine who had a right inferior frontal brain tumor resection in 2004? The diagnosis was Oligodendroglioma, WHO Grade II, but subsequent testing was negative for 1p/19q codeletion. The patient did not receive chemotherapy or radiation therapy; I have just been following him with surveillance imaging, and there still has been no sign at all of recurrence after almost 15 years. The tumor had a funny look on the preop scans, kind of ‘lumpy’ looking.”

Data for 4 Venn Diagram Spheres!

"Would you mind having a look at the pathology slides for a patient of mine who had a right inferior frontal brain tumor resection in 2004? The diagnosis was Oligodendroglioma, WHO Grade II, but subsequent testing was negative for 1p/19q codeletion. The patient did not receive chemotherapy or radiation therapy; I have just been following him with surveillance imaging, and there still has been no sign at all of recurrence after almost 15 years. The tumor had a funny look on the preop scans, kind of 'lumpy' looking."

8 Data Spheres of the Venn Diagram Model for Oncologic Integrated Diagnosis

- Age
- Gender
- **History**
- **Anatomic Location** (including Neurosurgeon intraop findings)
- **Imaging Characteristics** (CT, MRI, PET, MRS, Perfusion Studies)
- **Histologic Features** (Cytologic prep, Frozen section, FFPE)
- **Differentiation Markers** (IHC)
- **Molecular Signature** (IHC / FISH / PCR / NGS / Methylation Profiling)

8 Data Spheres of the Venn Diagram Model for Oncologic Integrated Diagnosis

- Age
- Gender
- **History: No Rx; 15 years of PFS**
- **Anatomic Location: Inferior frontal lobe**
- **Imaging Characteristics: "Lumpy"**
- **Histologic Features: Oligodendroglioma**
- **Differentiation Markers** (IHC)
- **Molecular Signature** (IHC / FISH / PCR / NGS / Methylation Profiling)

For the prepared mind, the most likely diagnosis can be reached from the data in these 4 spheres!

...without looking at a single H&E slide!

My response (less than 5 minutes after reading the email)

I just looked at the preop imaging

My response (less than 5 minutes after reading the email)

I just looked at the preop imaging - my assistant has requested the slides, and I'll certainly look at them when they come in

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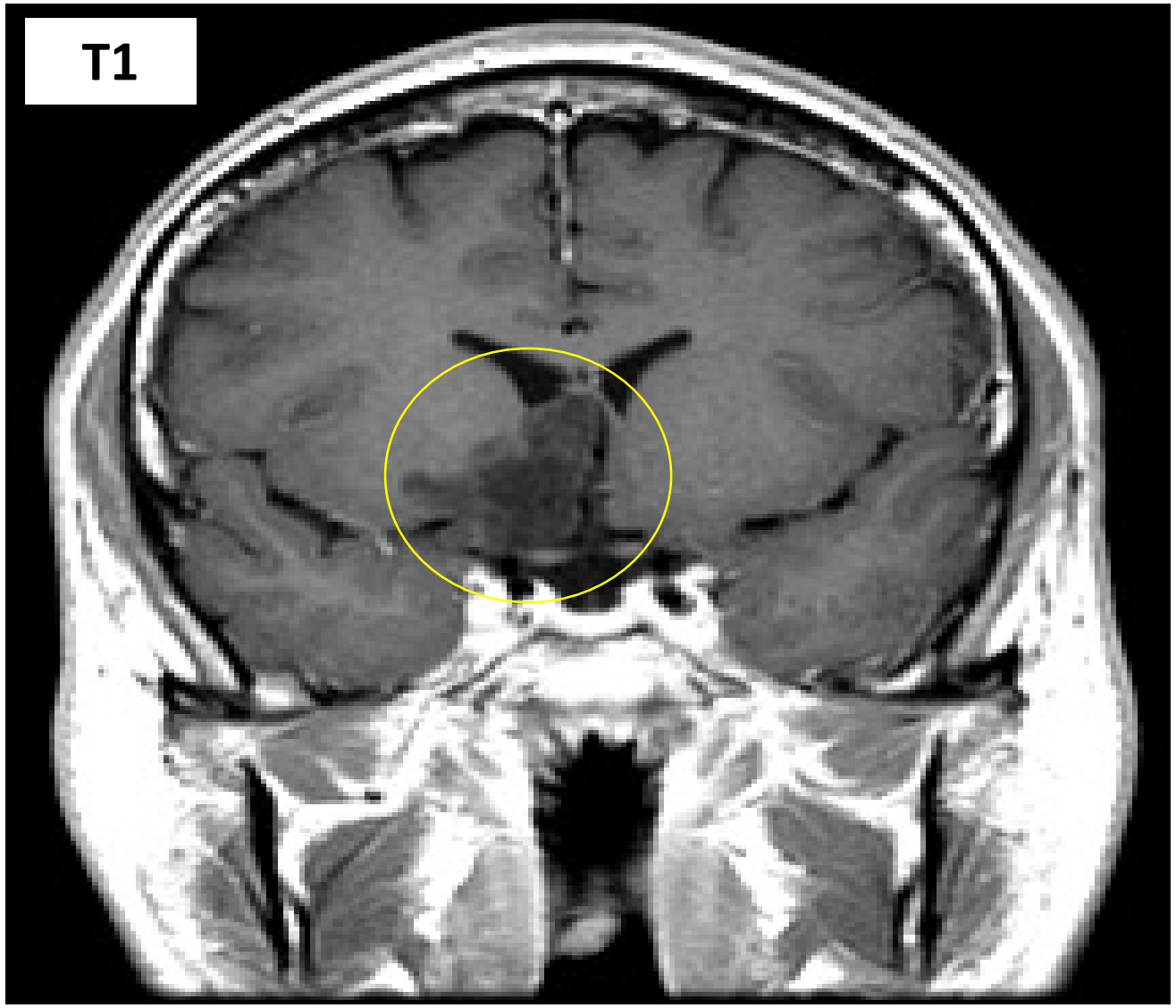
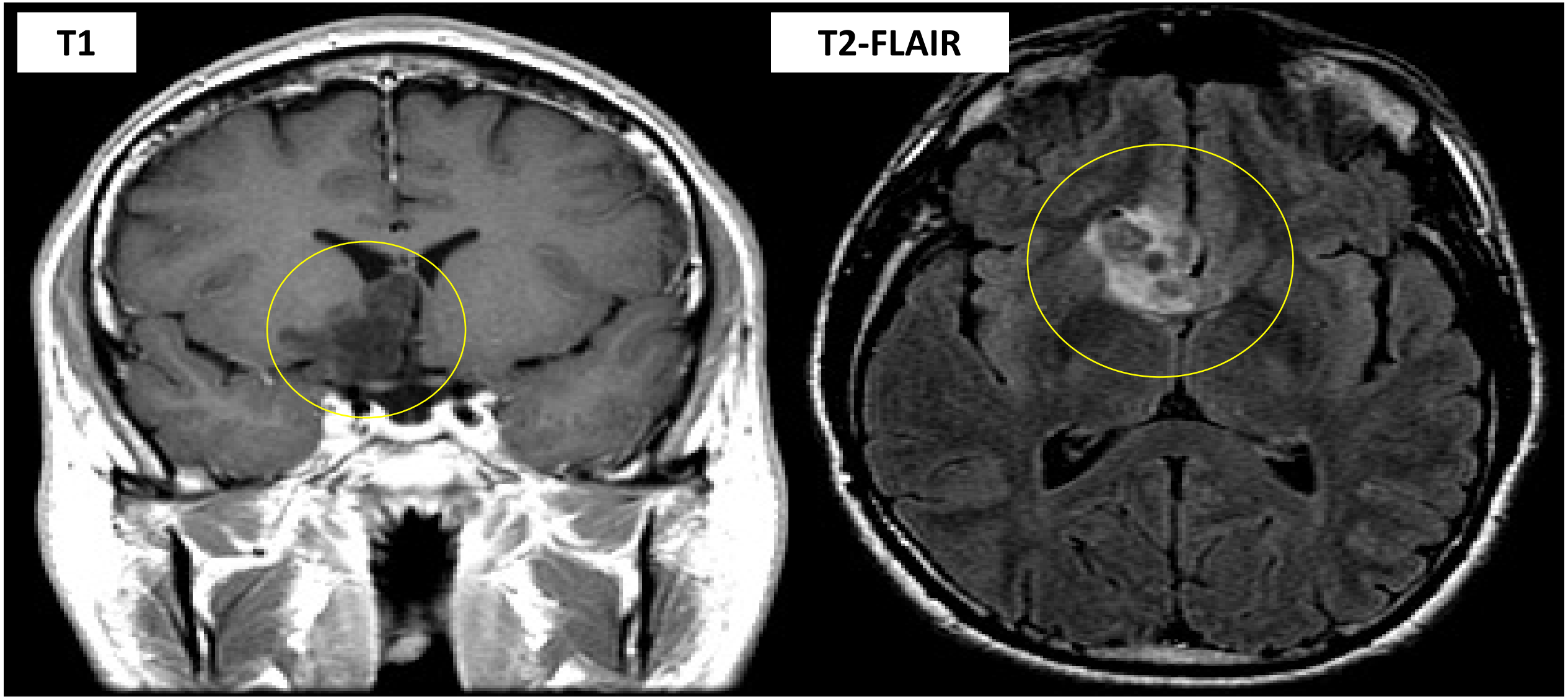
It's a **Septal-Caudate DNET**

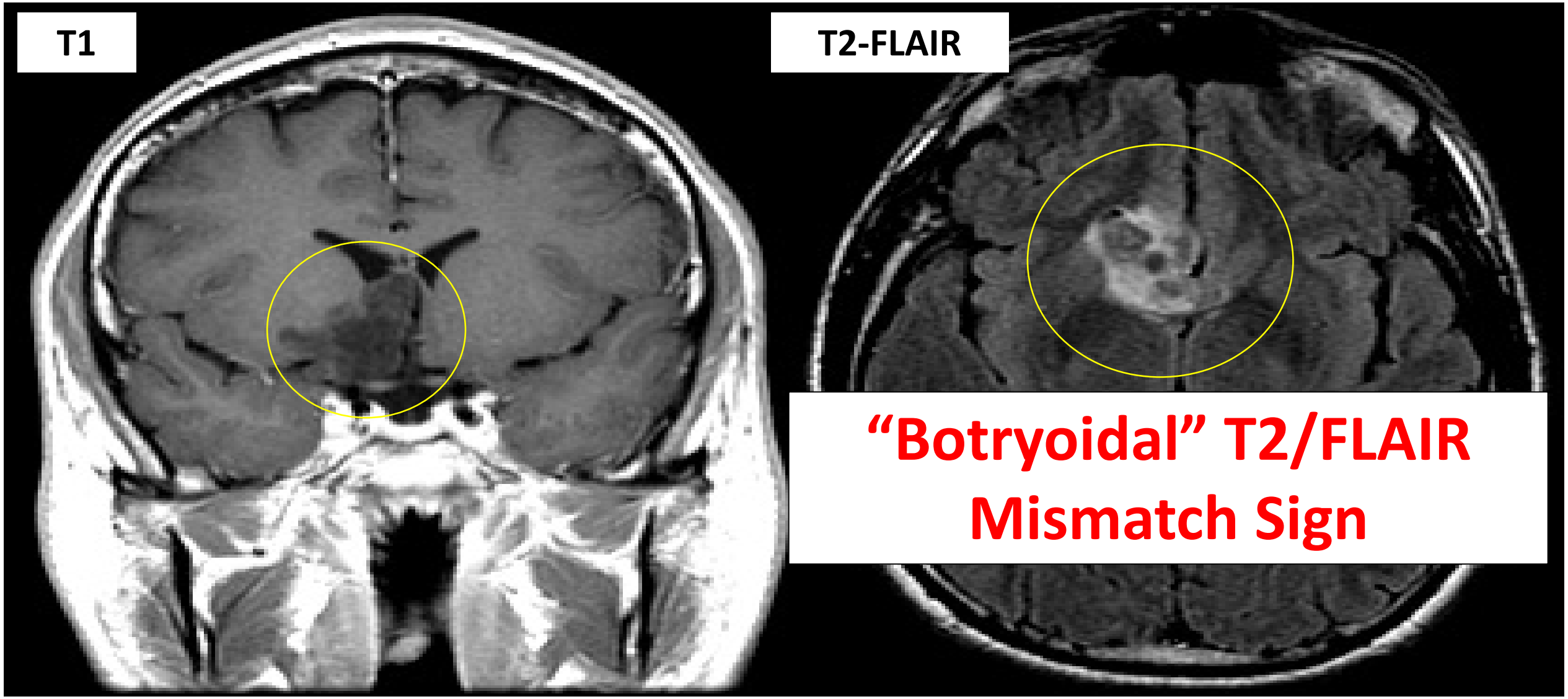
My response (less than 5 minutes after reading the email)

I just looked at the preop imaging - my assistant has requested the slides, and I'll certainly look at them when they come in, but **I already know what it is** - in my humble opinion **the preop MR imaging is diagnostic**

It's a **Septal-Caudate DNET (Myxoid Glioneuronal Tumor)**


T1


T1
T2-FLAIR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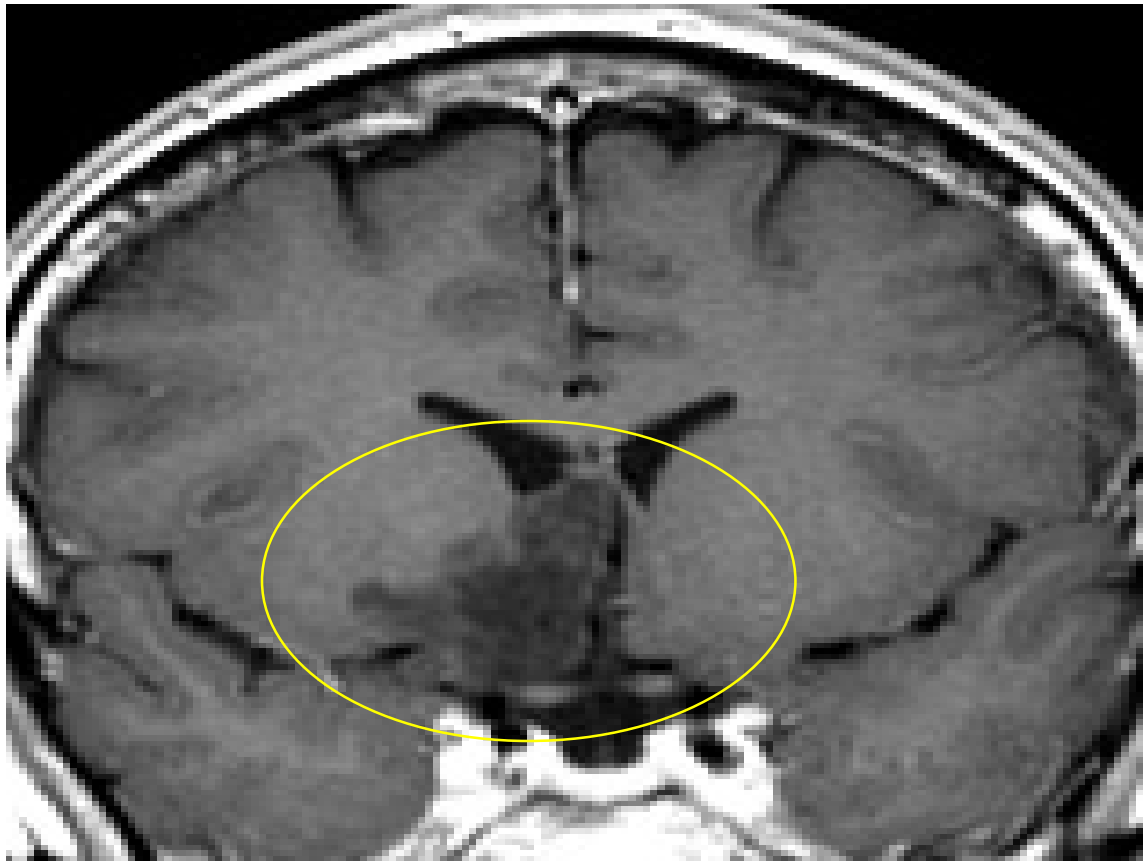
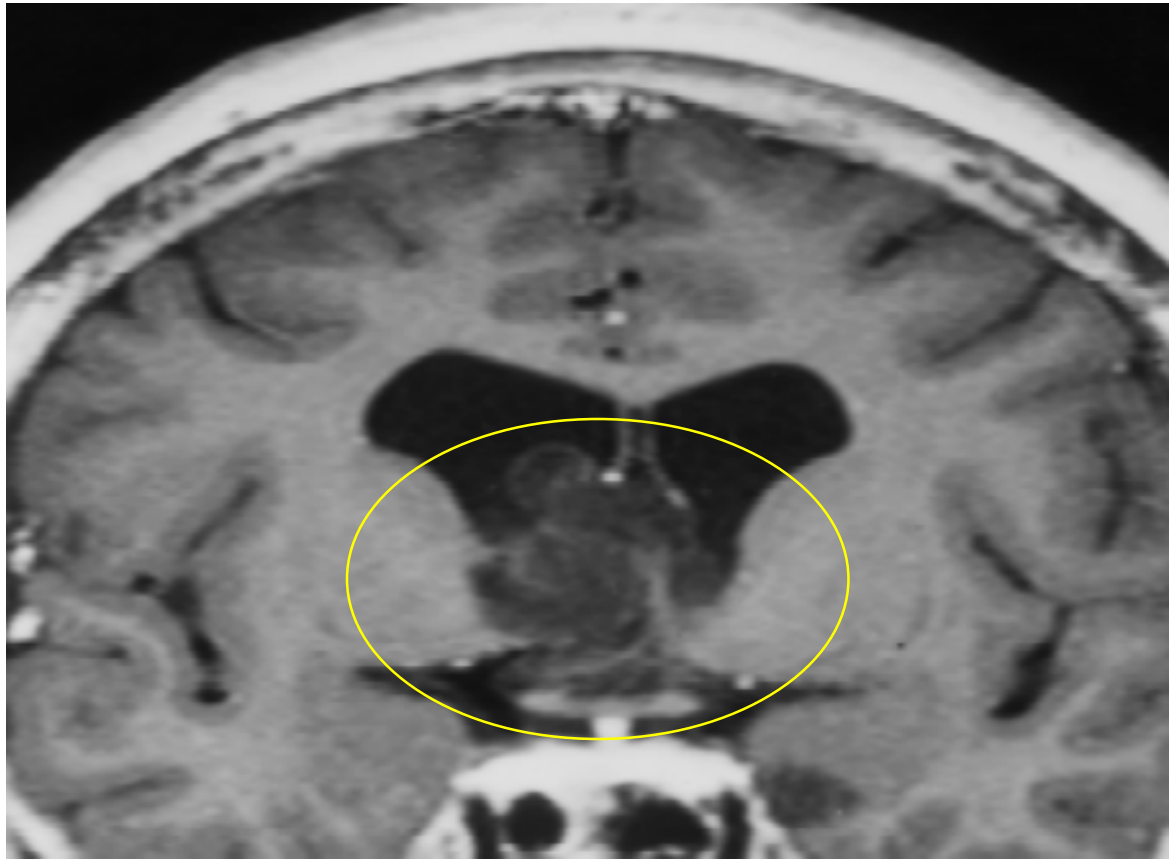
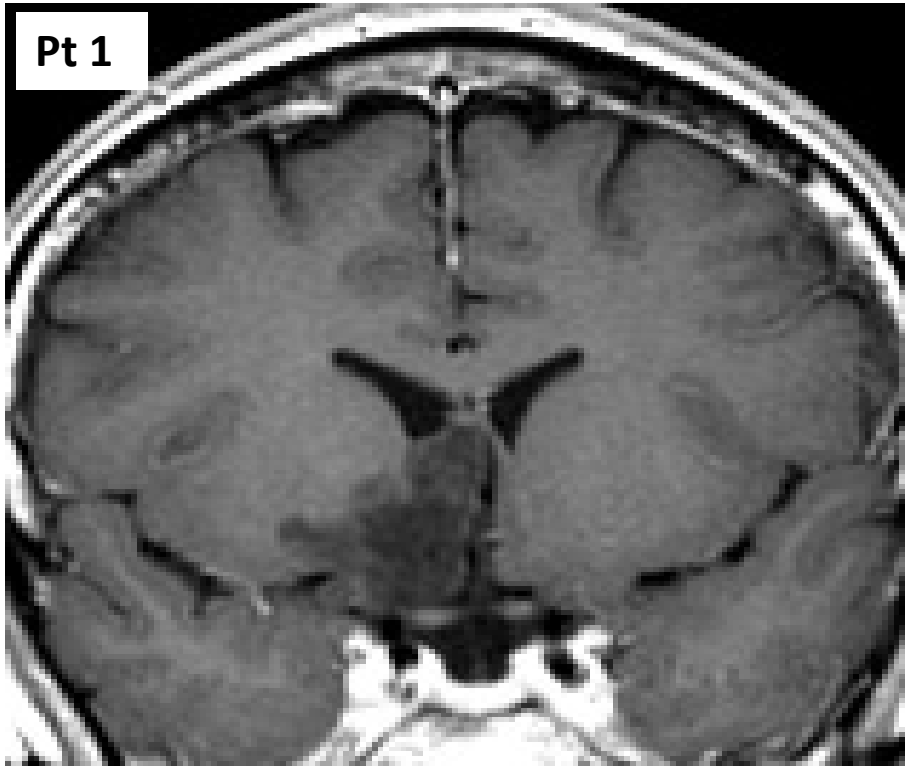
T2-FLAIR
“Botryoidal” T2/FLAIR
Mismatch Sign

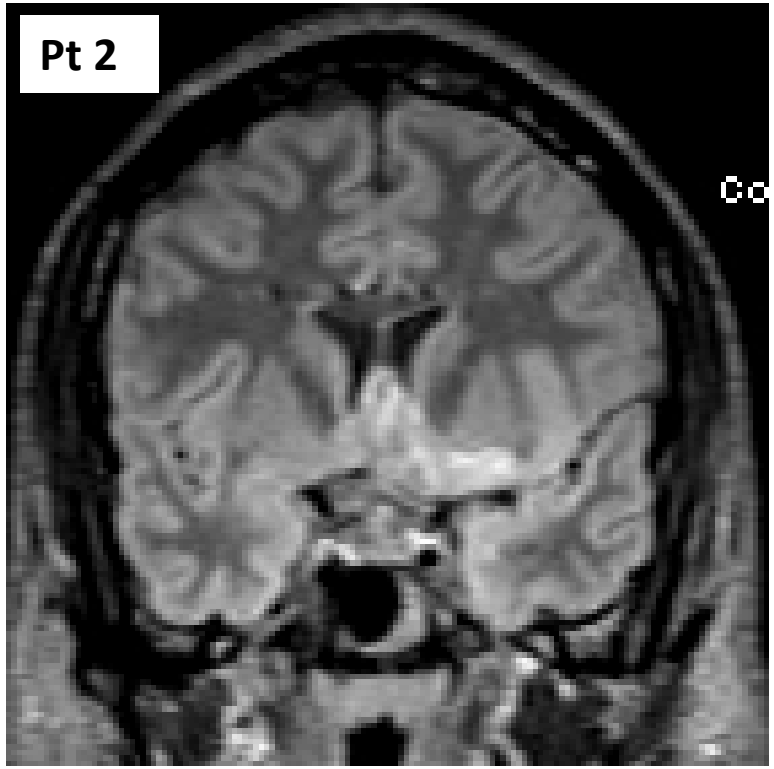
MDACC

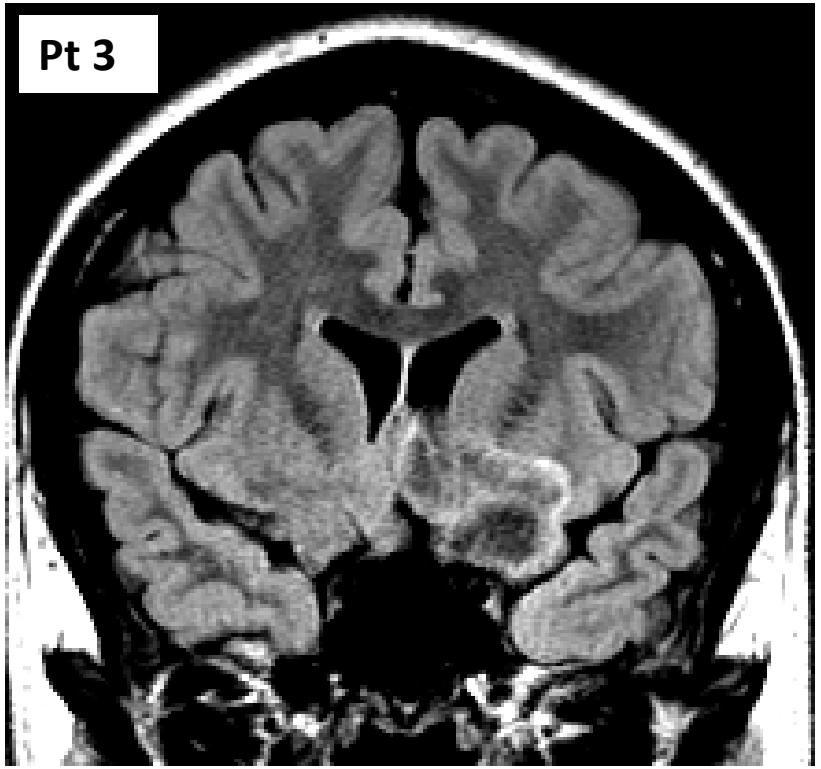


Baisden *AJSP* PMID 11257624









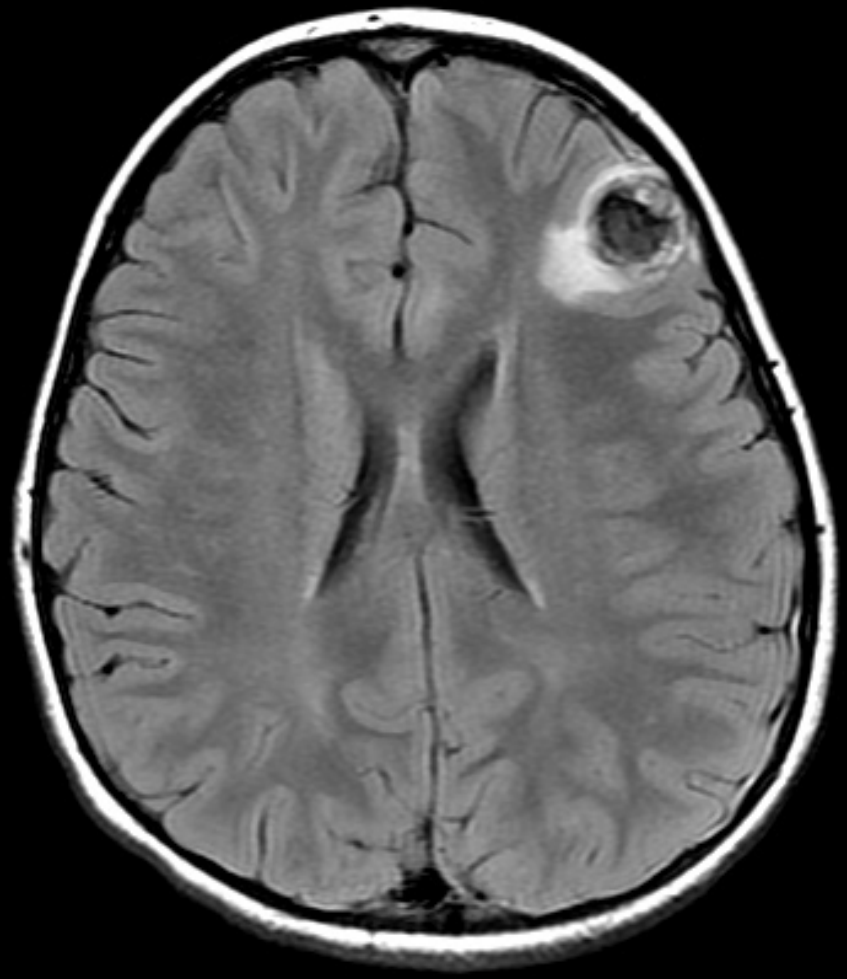
Coronal plane - centered in the septal nuclei
Larger examples expand dorsally into the lateral ventricle and ventrolaterally, undercutting the basal ganglia in an "L-Shaped" or "Hockey Stick" configuration

Patient 6

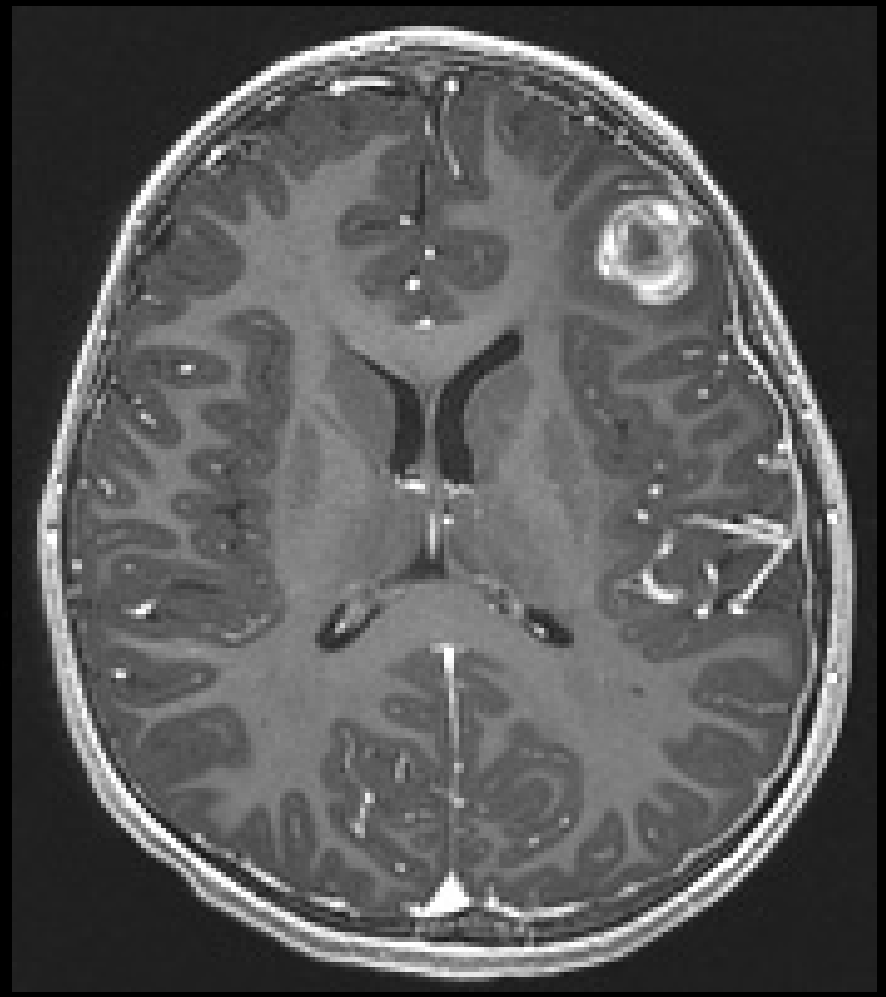
5-year-old male

IMAGING

T1



T1 + C



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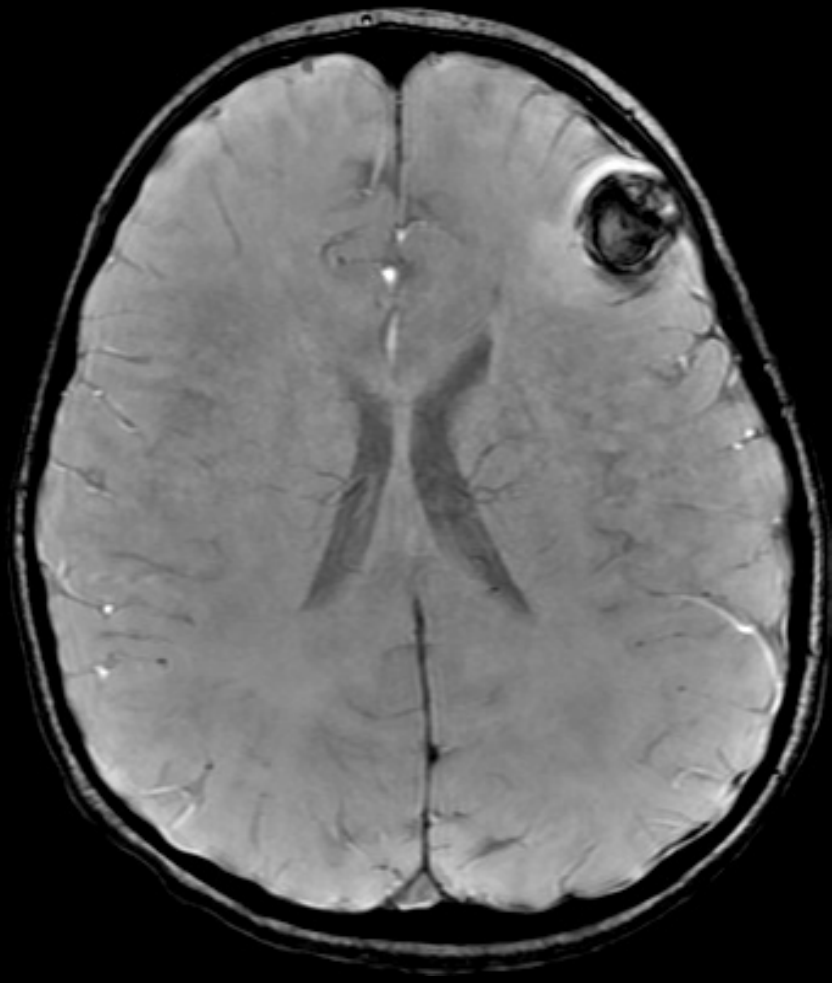
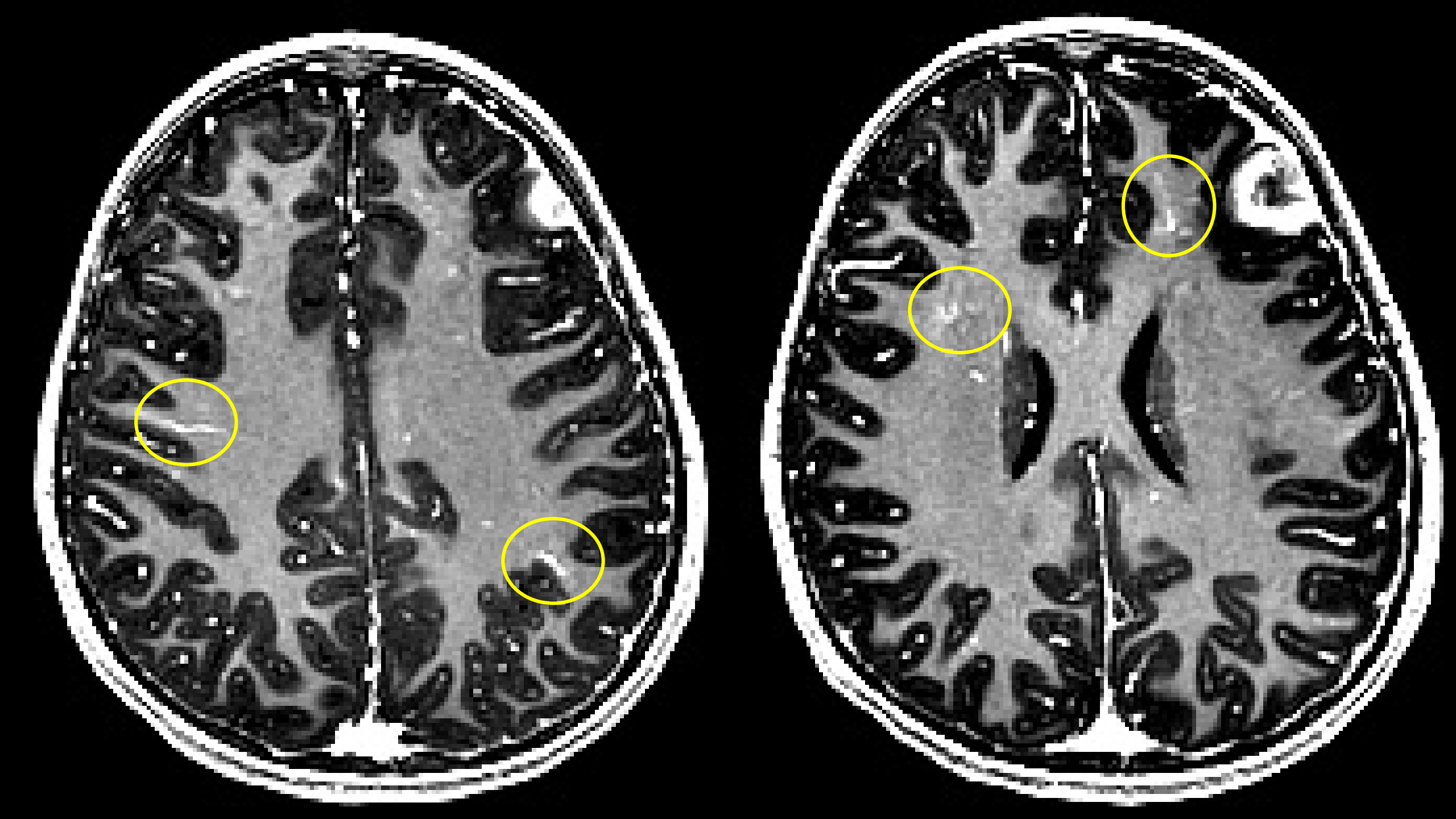
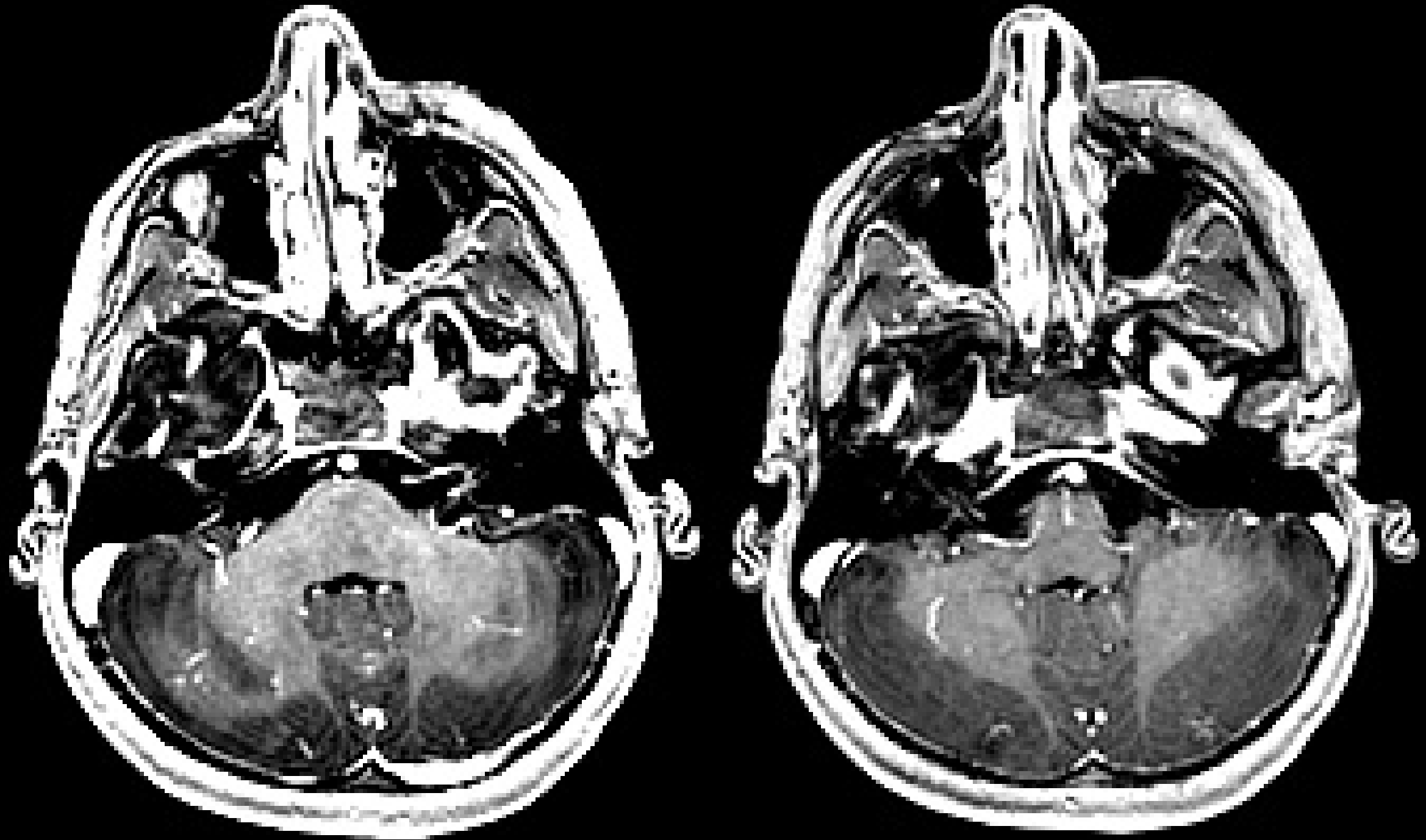
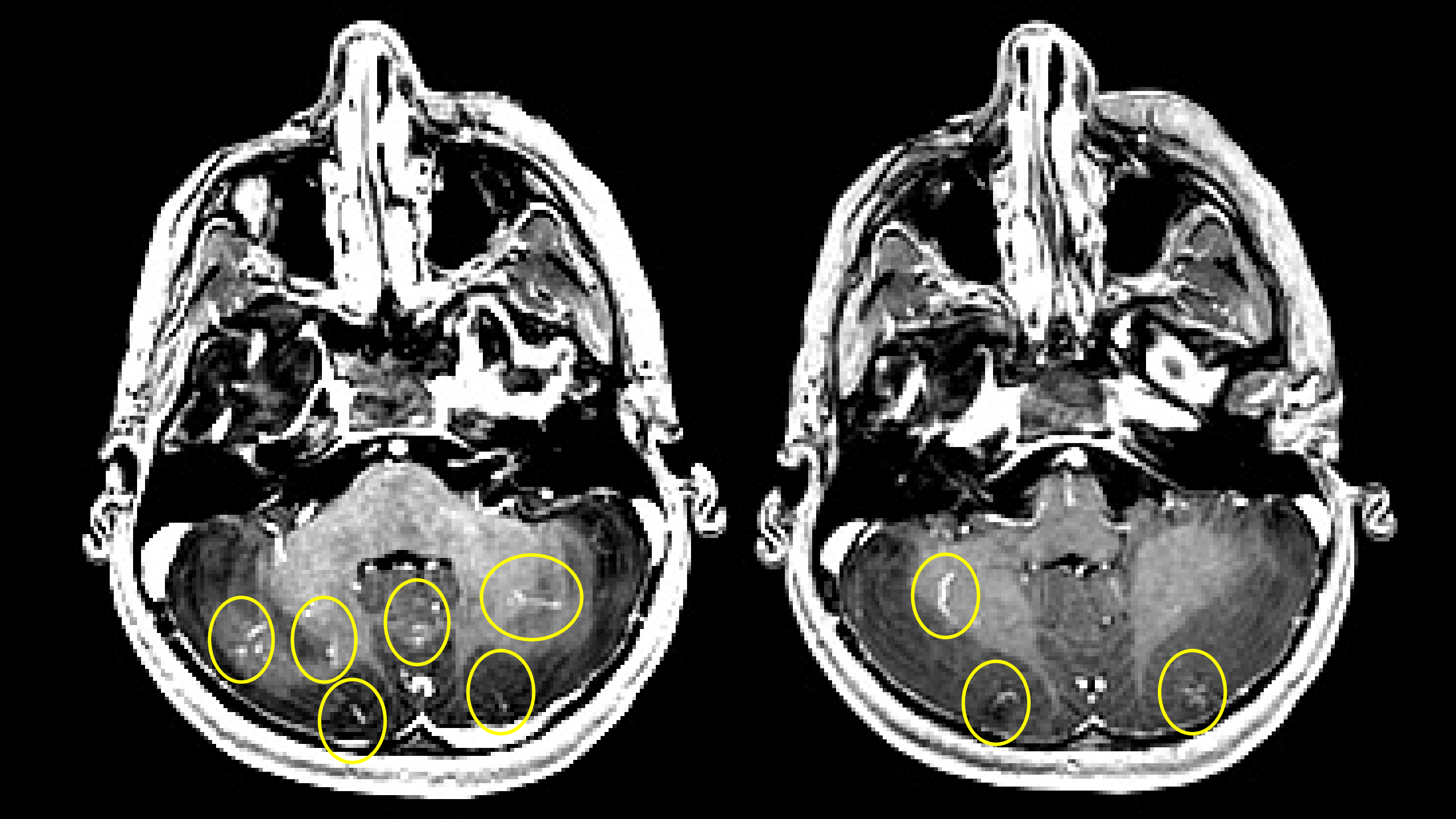
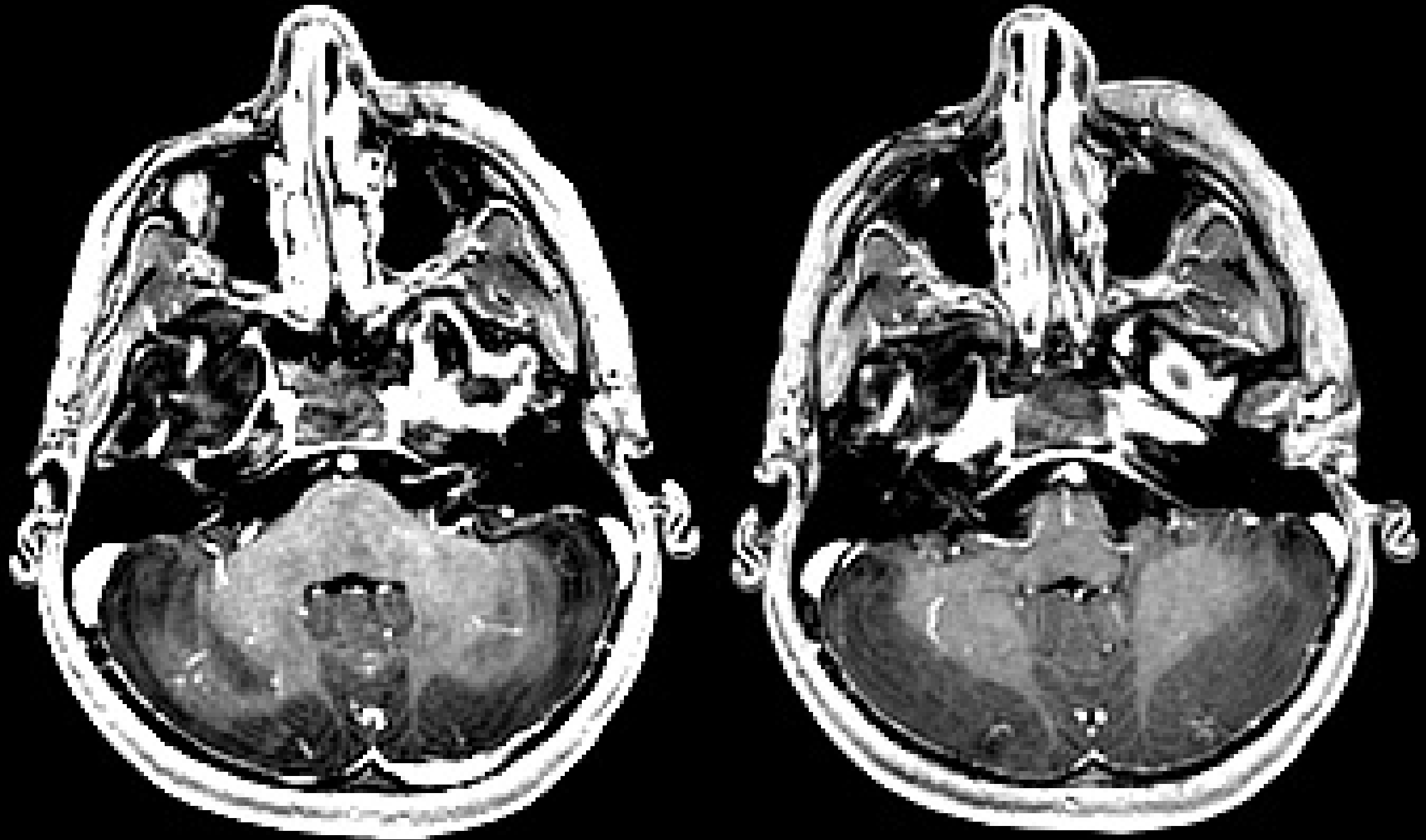








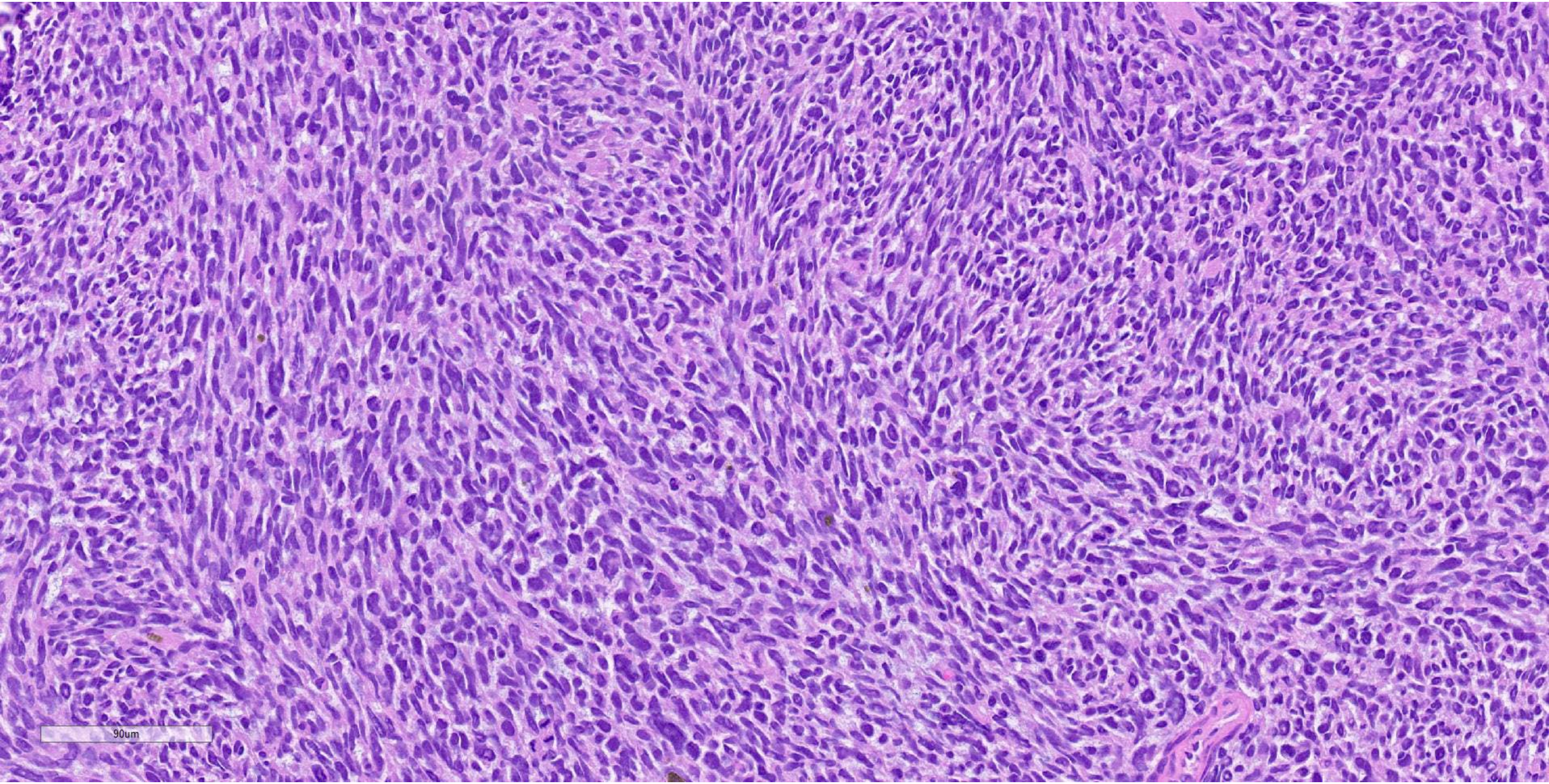


Multiple Bilateral Supratentorial and Infratentorial DVAs

Developmental Venous Anomalies

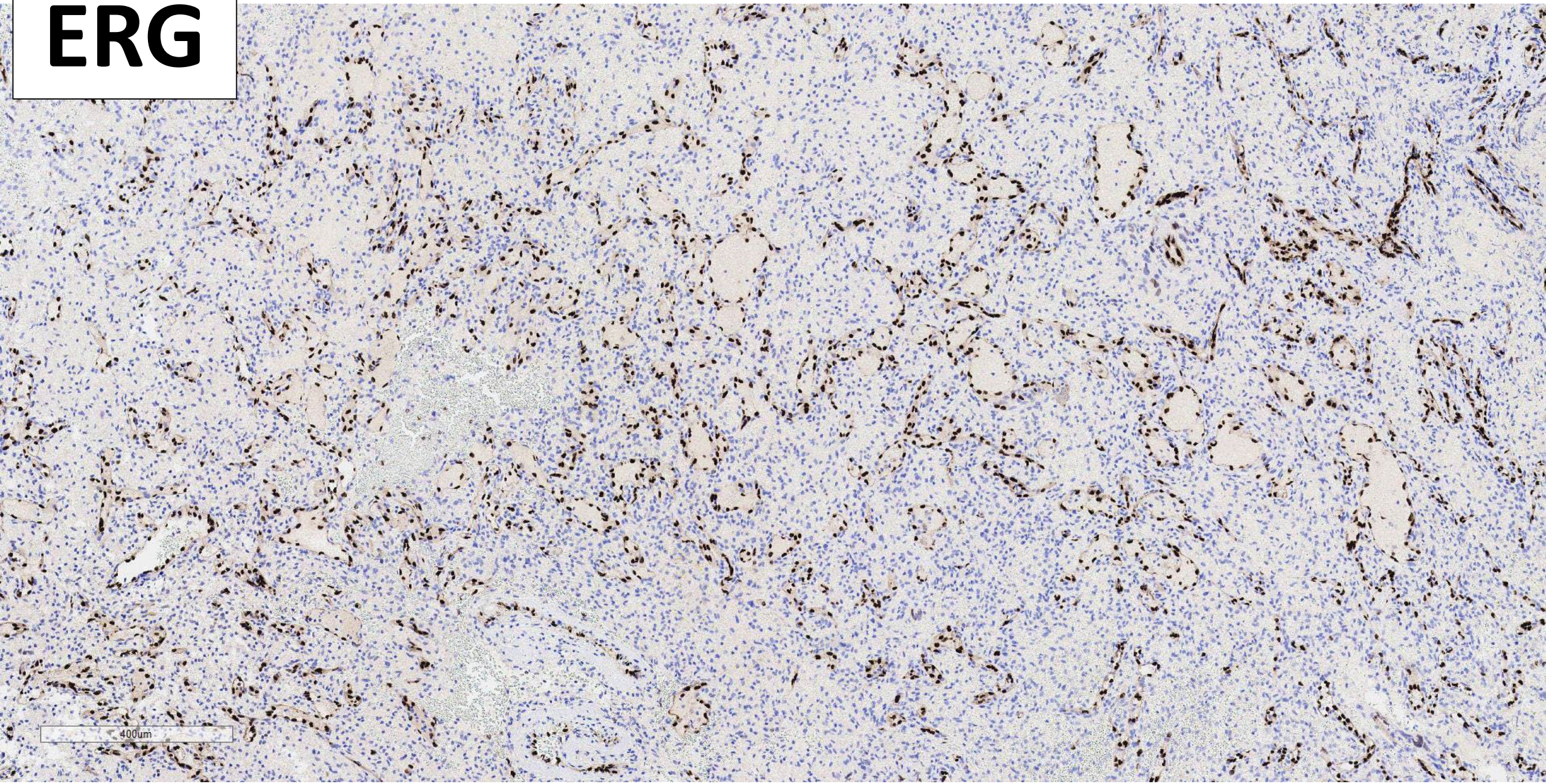
DIAGNOSIS?

Histology


90um

DIAGNOSIS?

ERG



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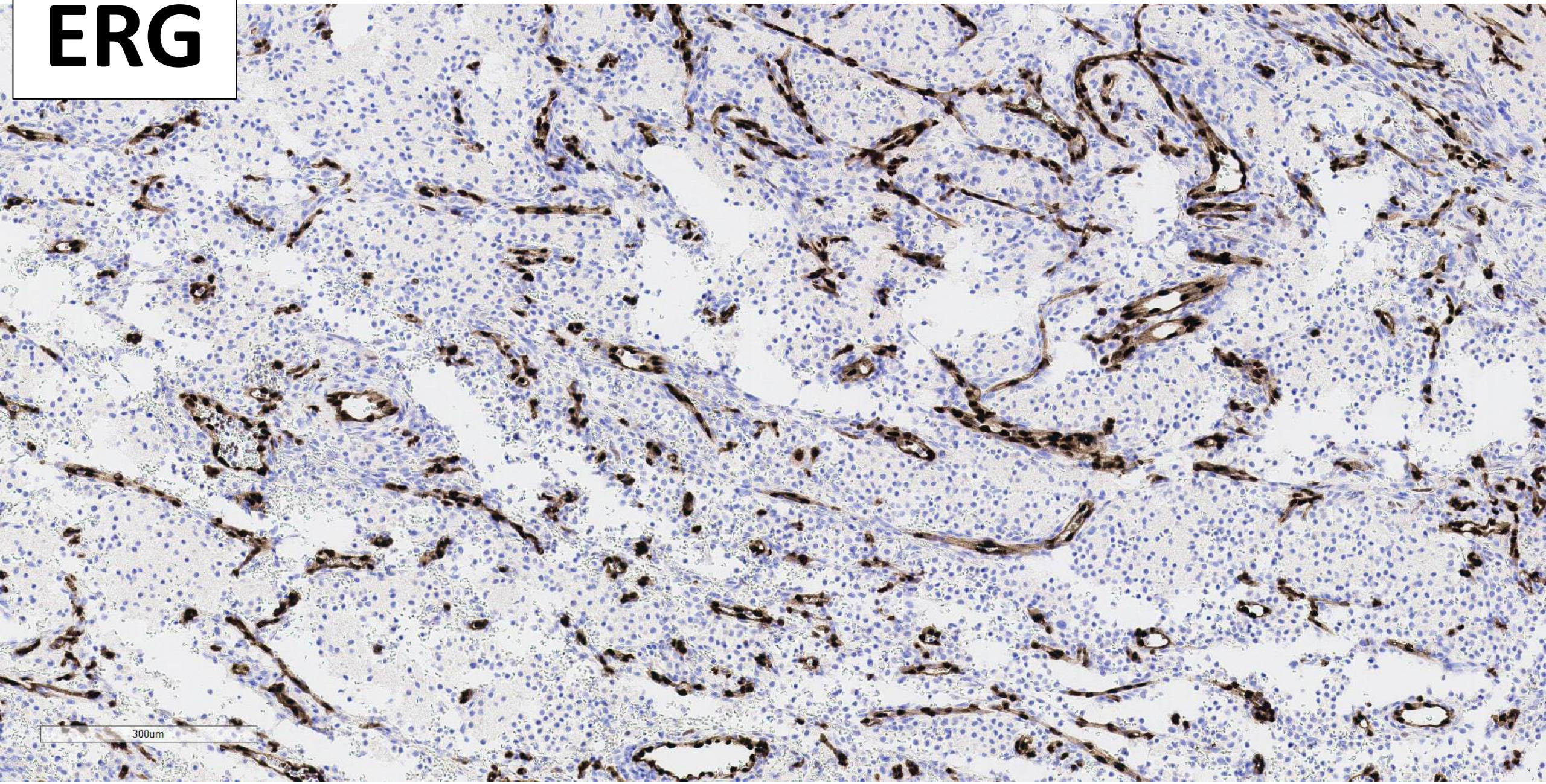
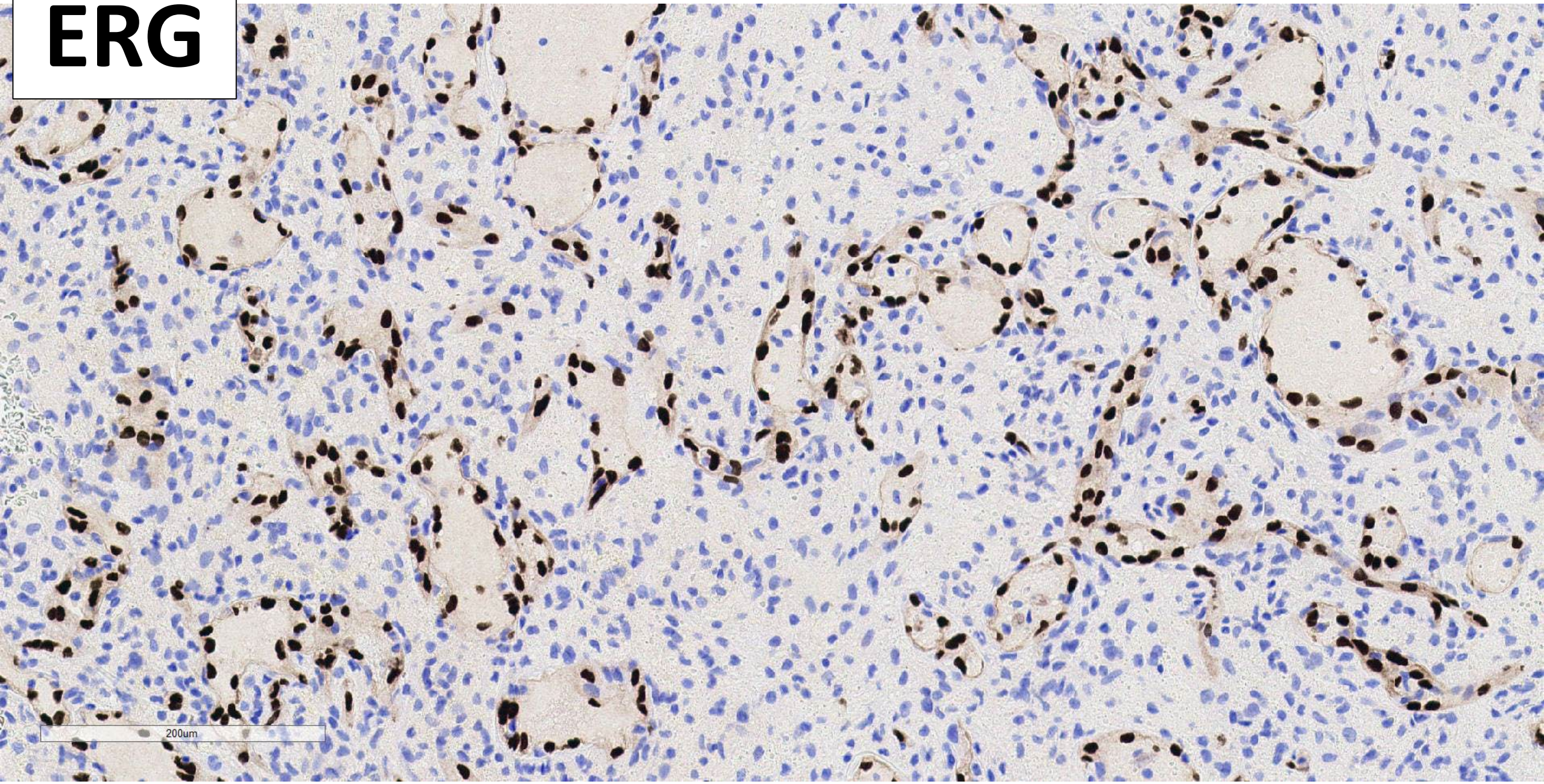
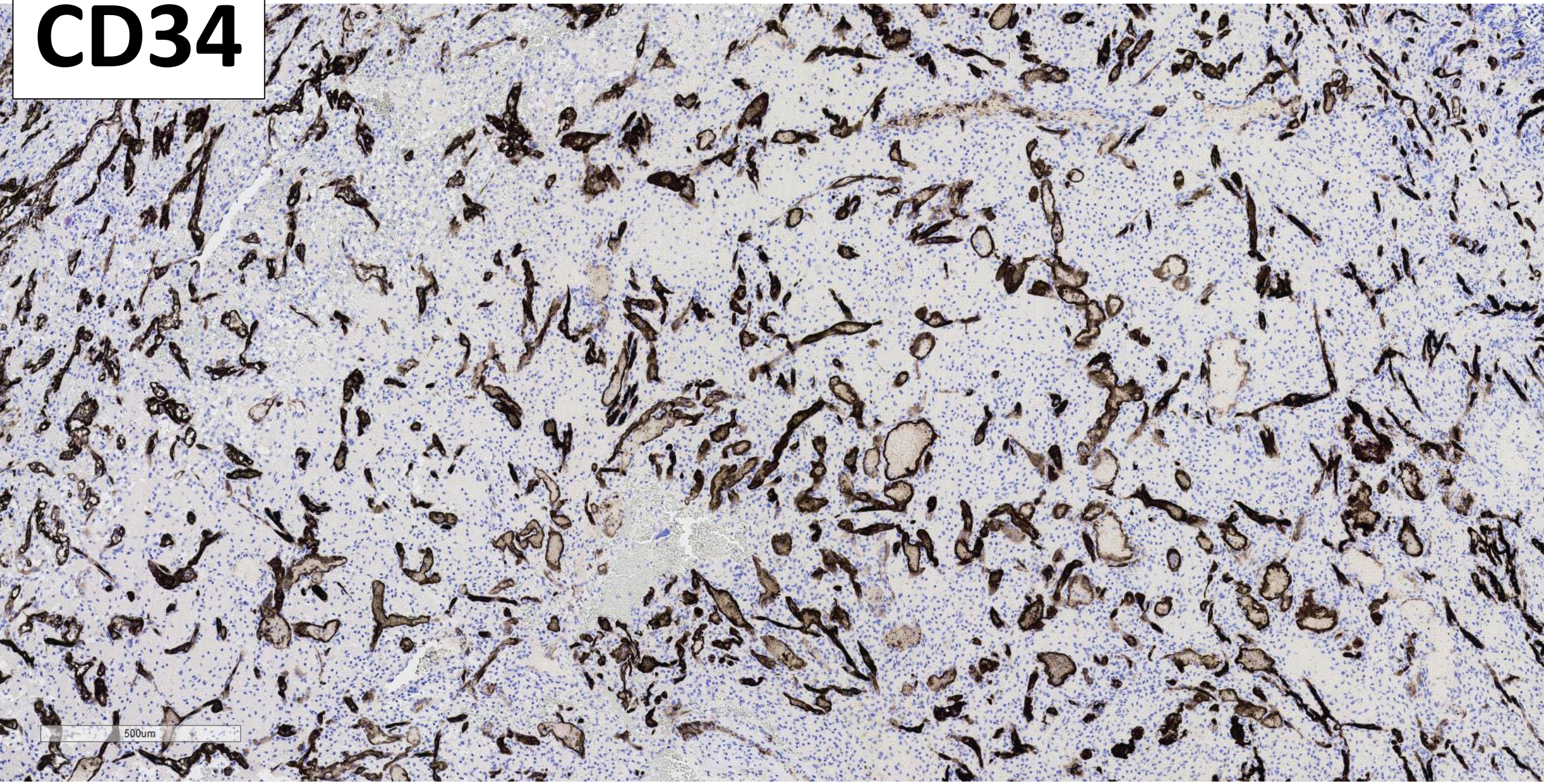
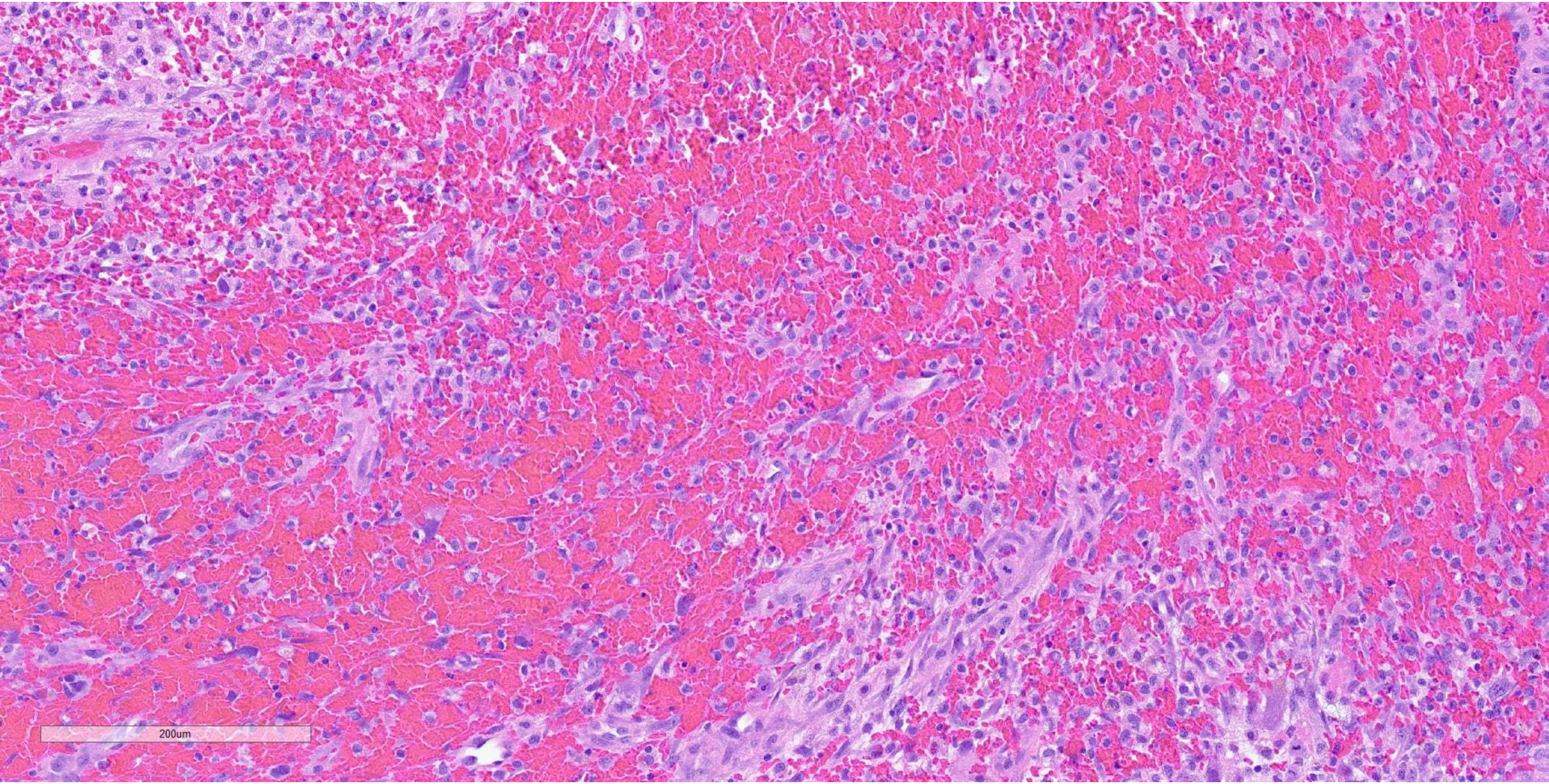


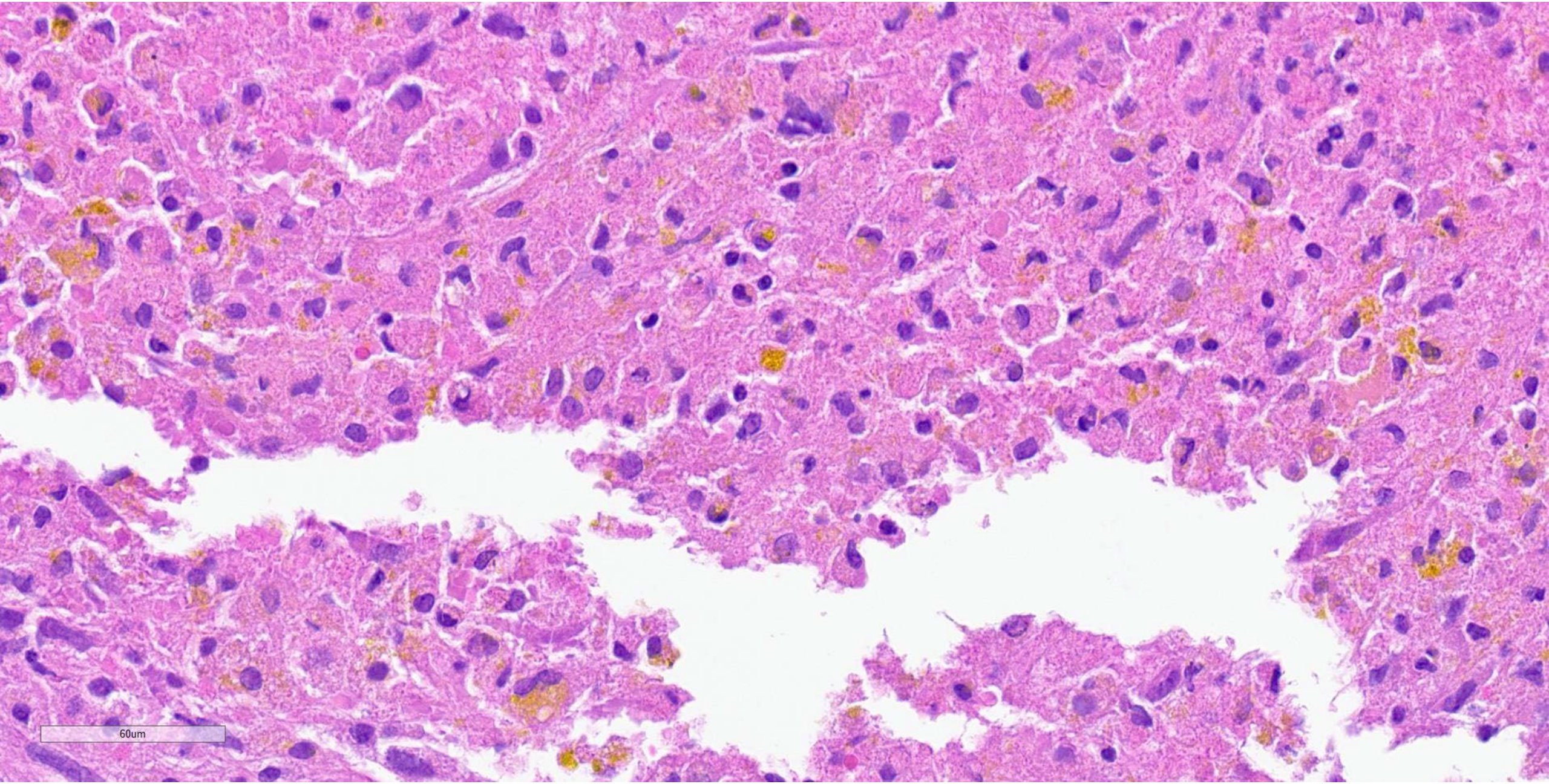
ERG



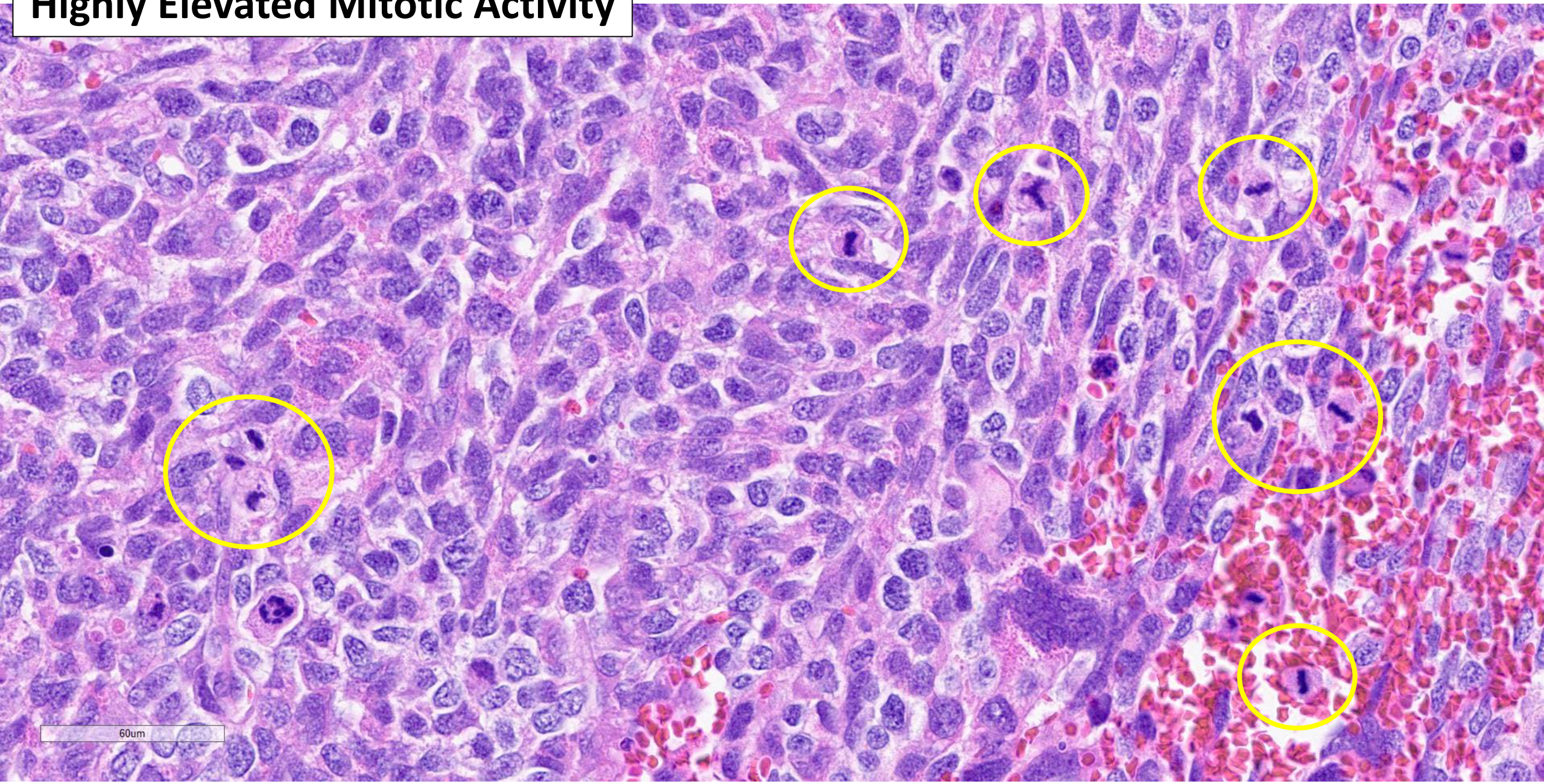
CD34



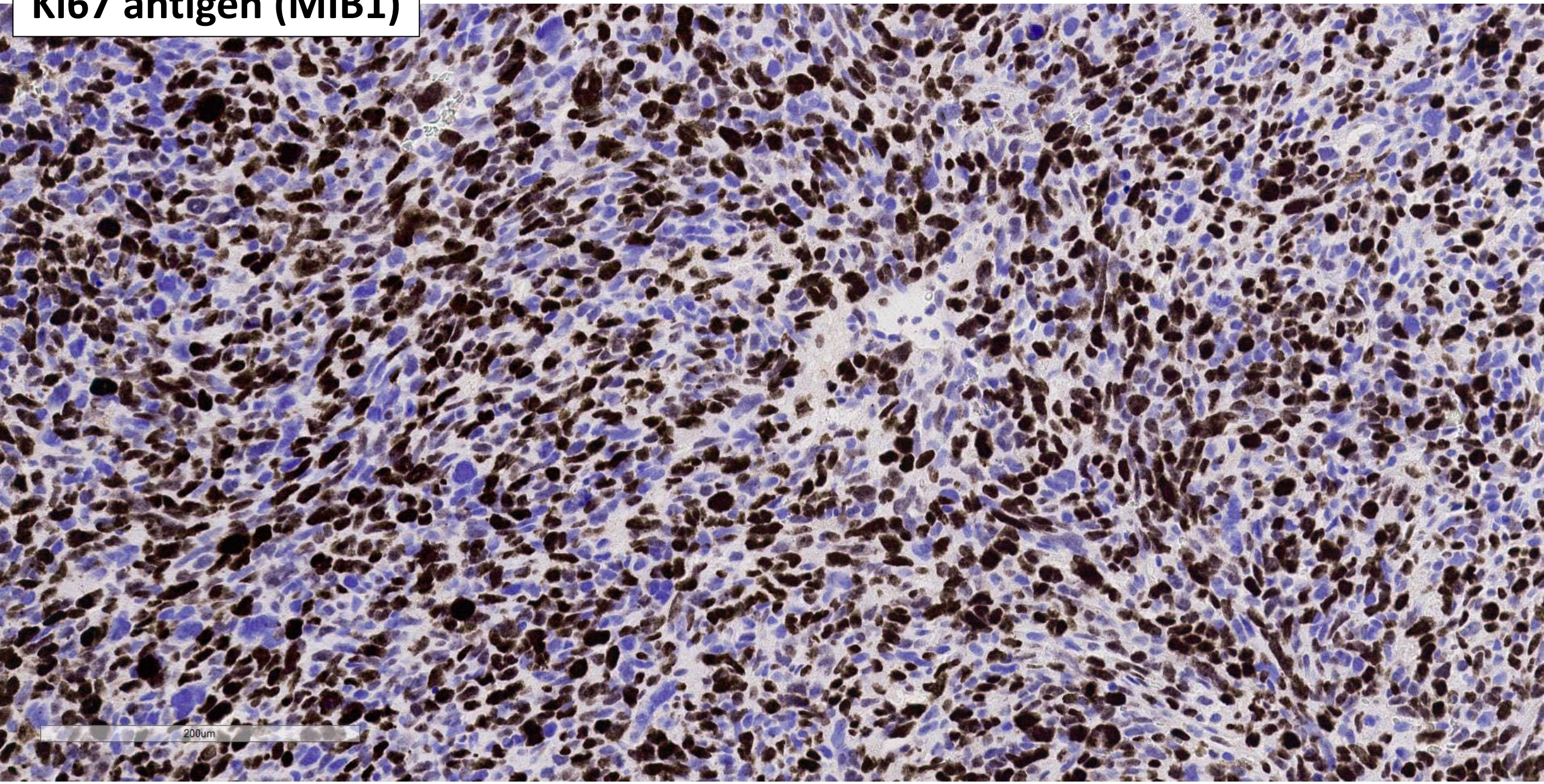

200um

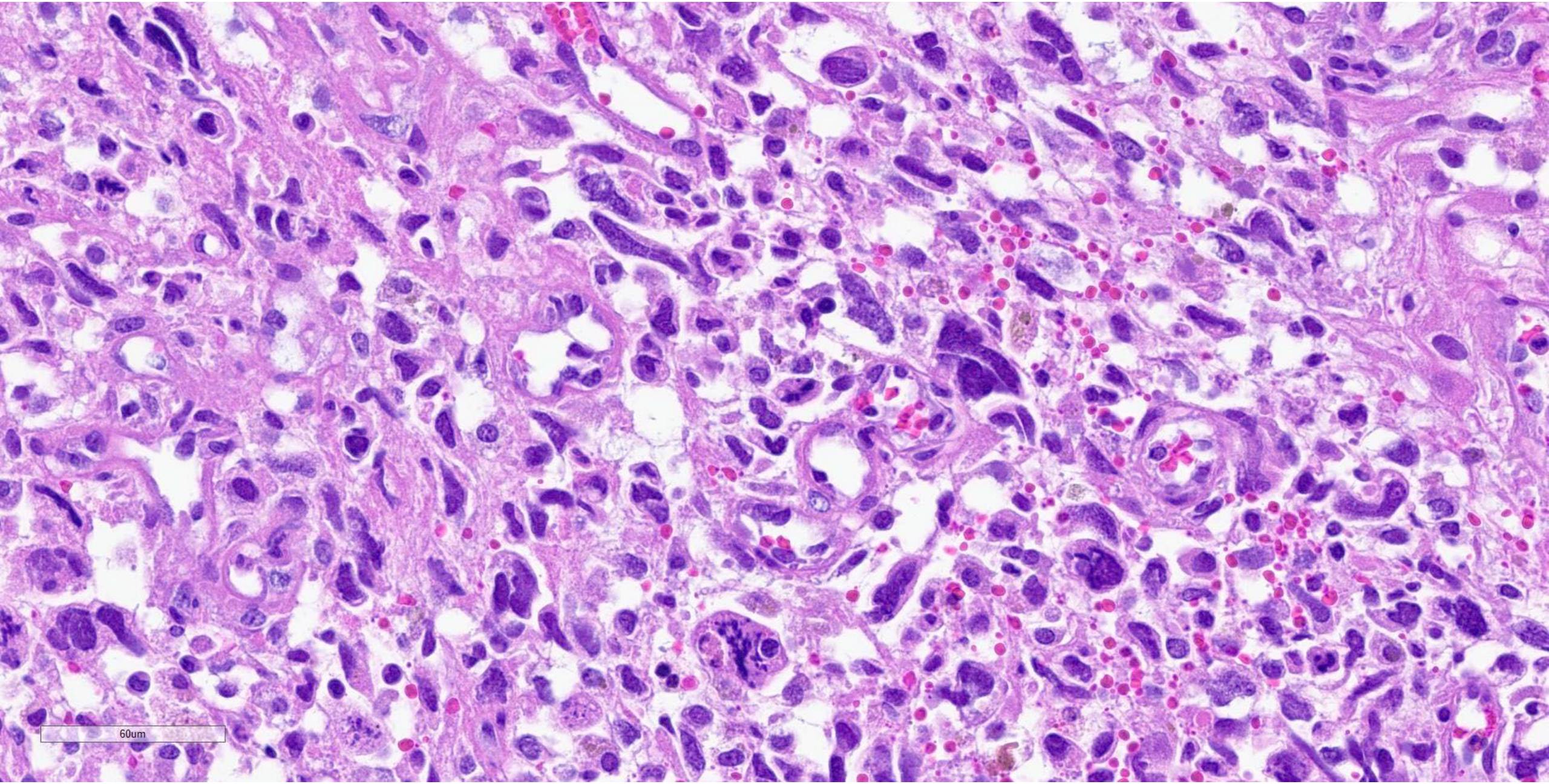

60um

Highly Elevated Mitotic Activity



Ki67 antigen (MIB1)

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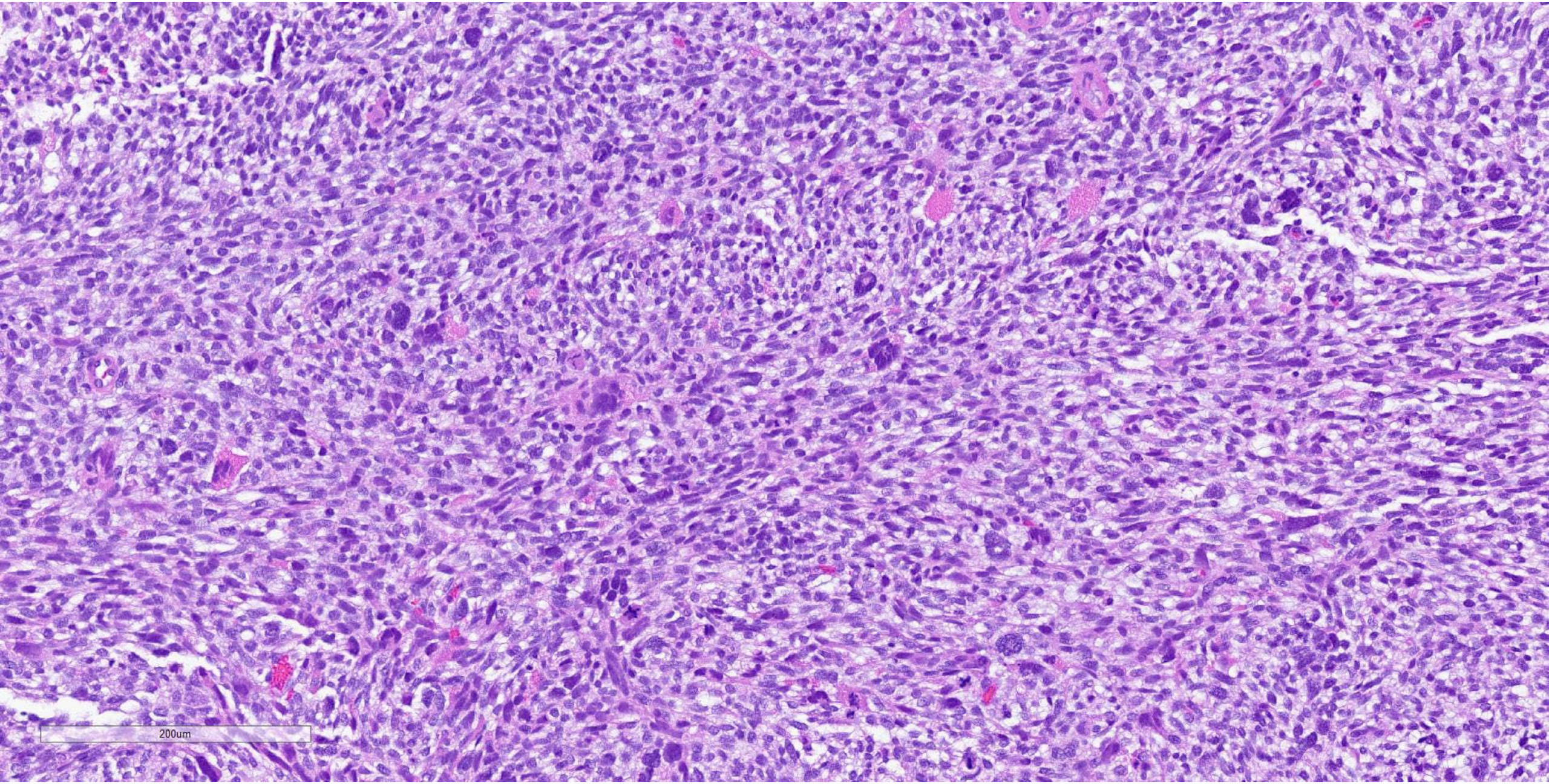
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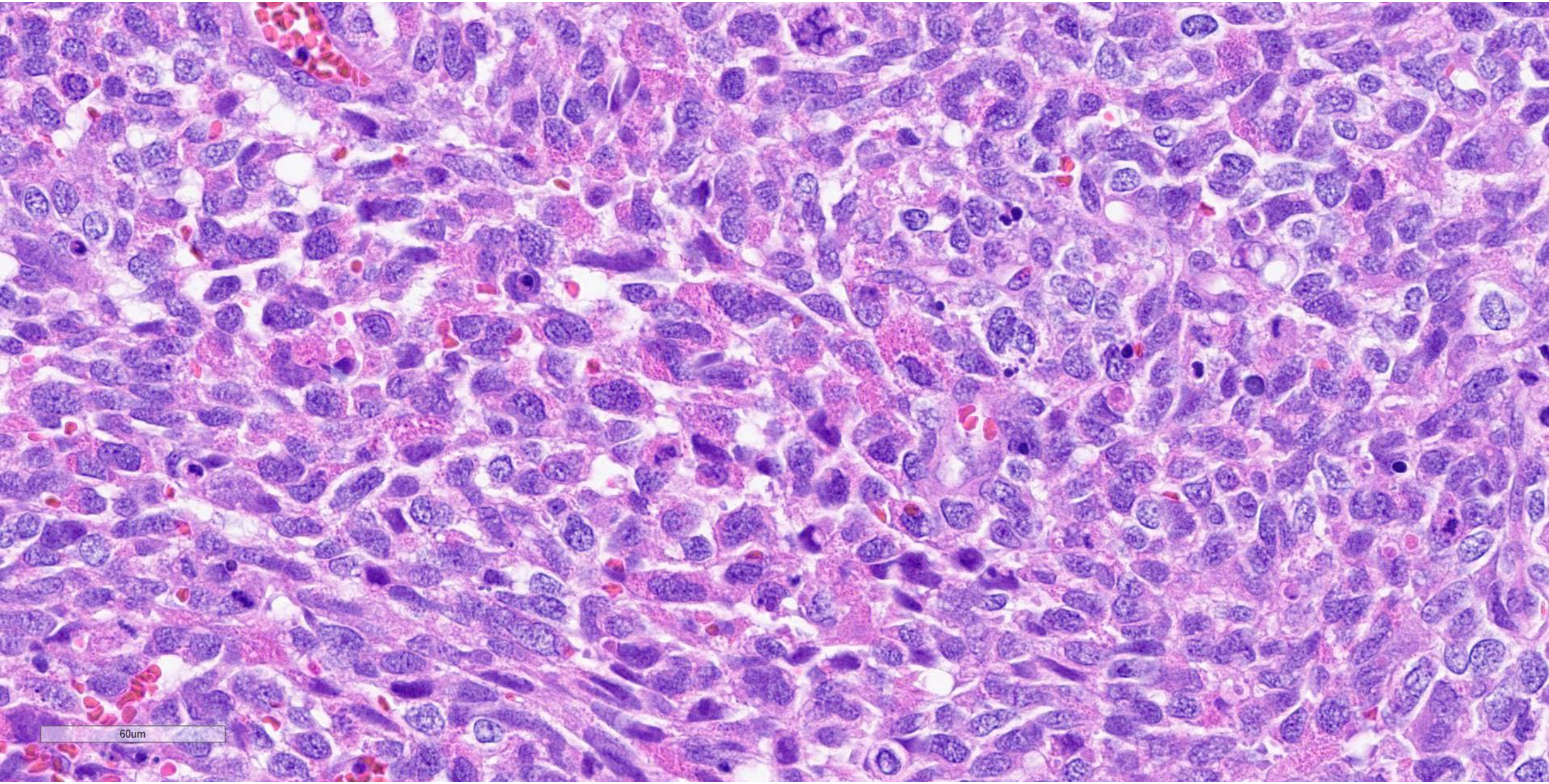
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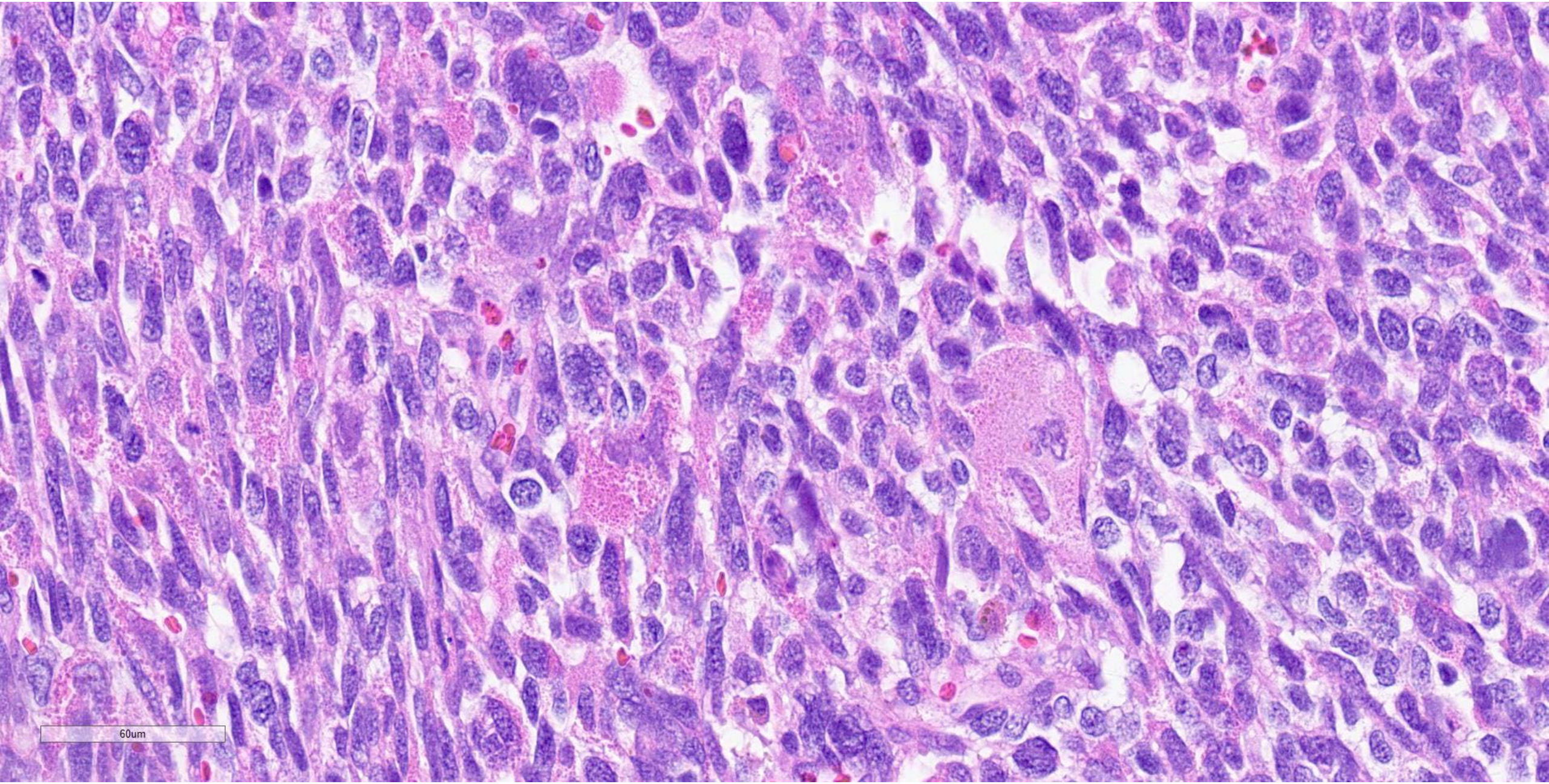
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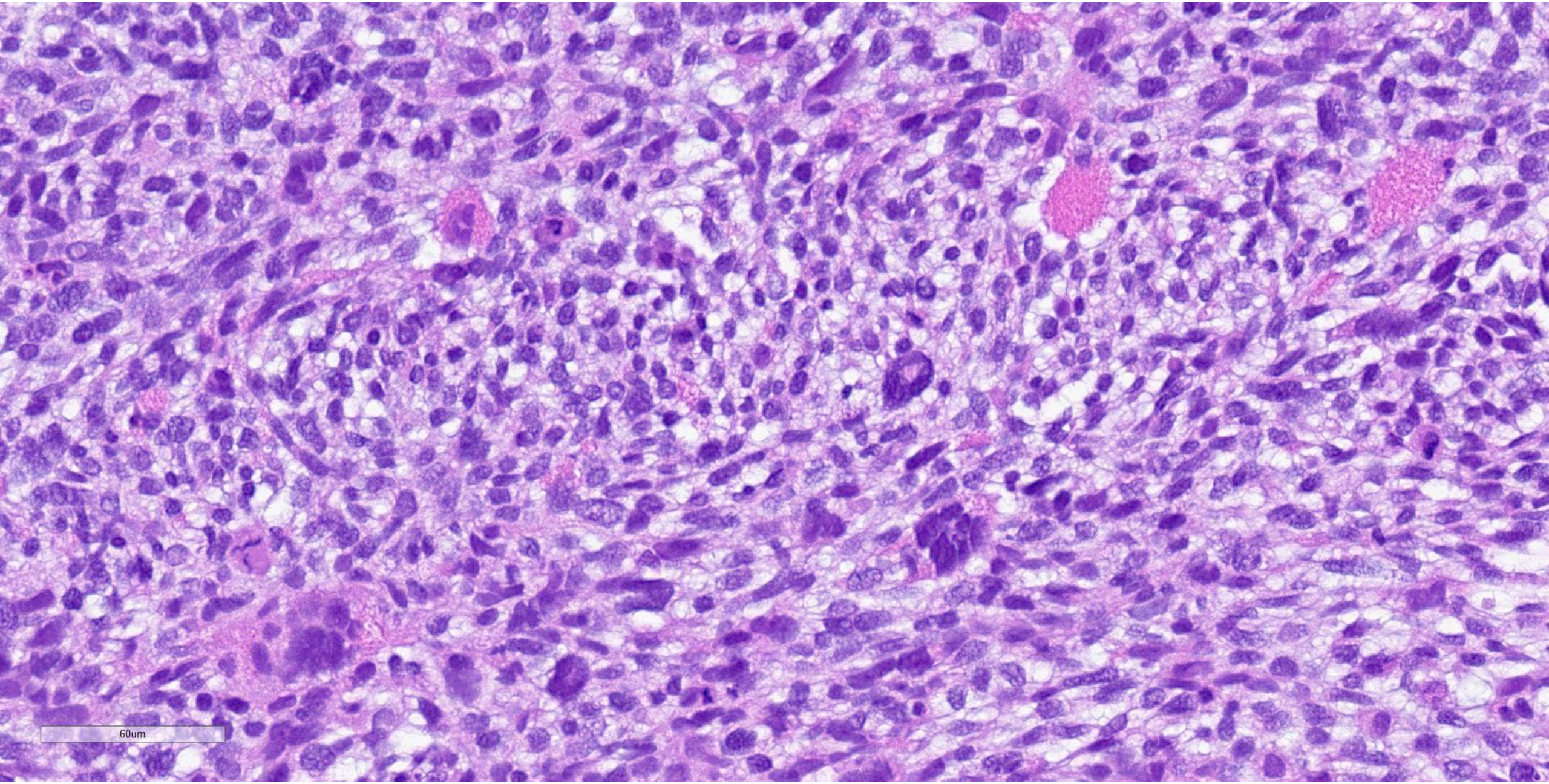
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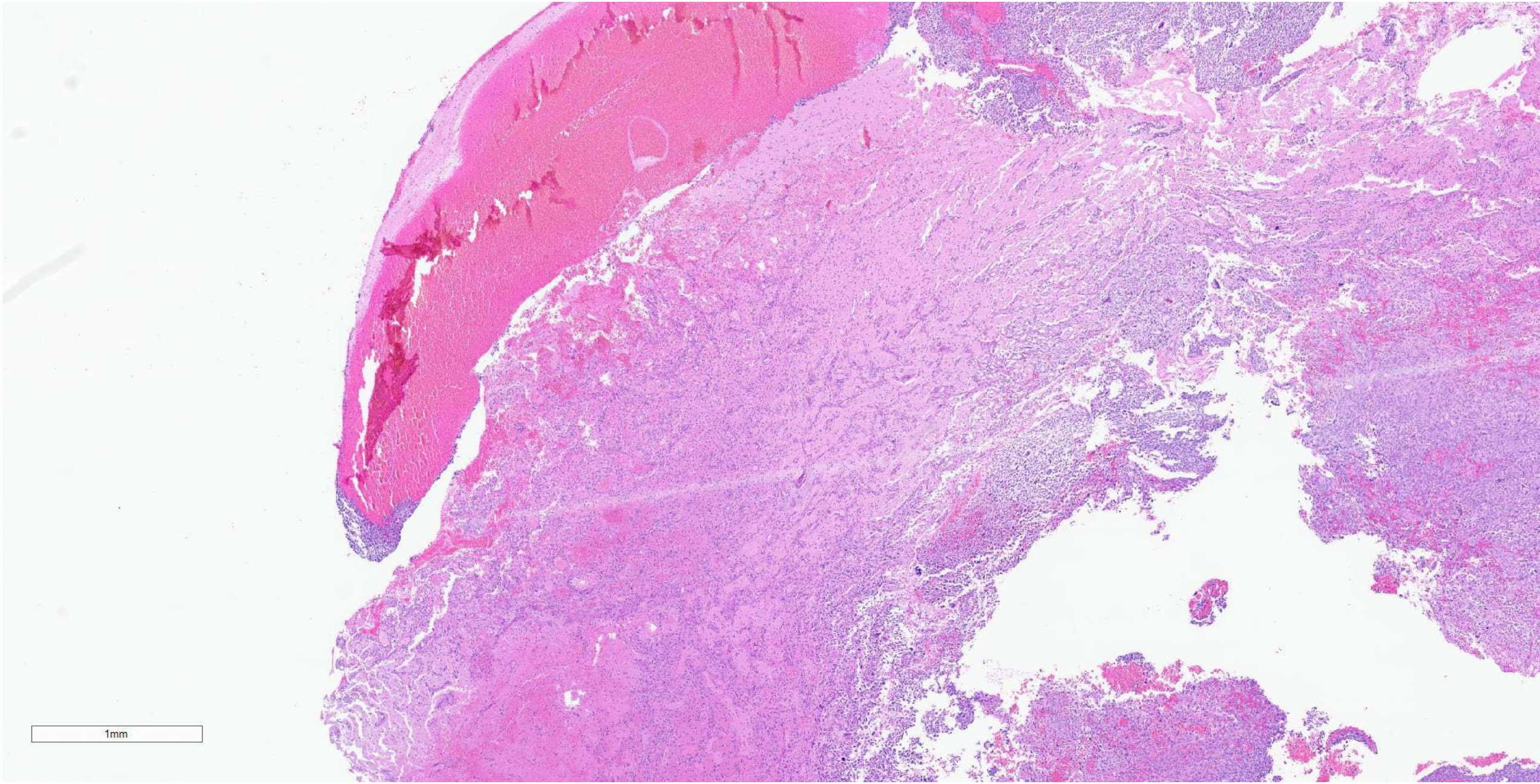
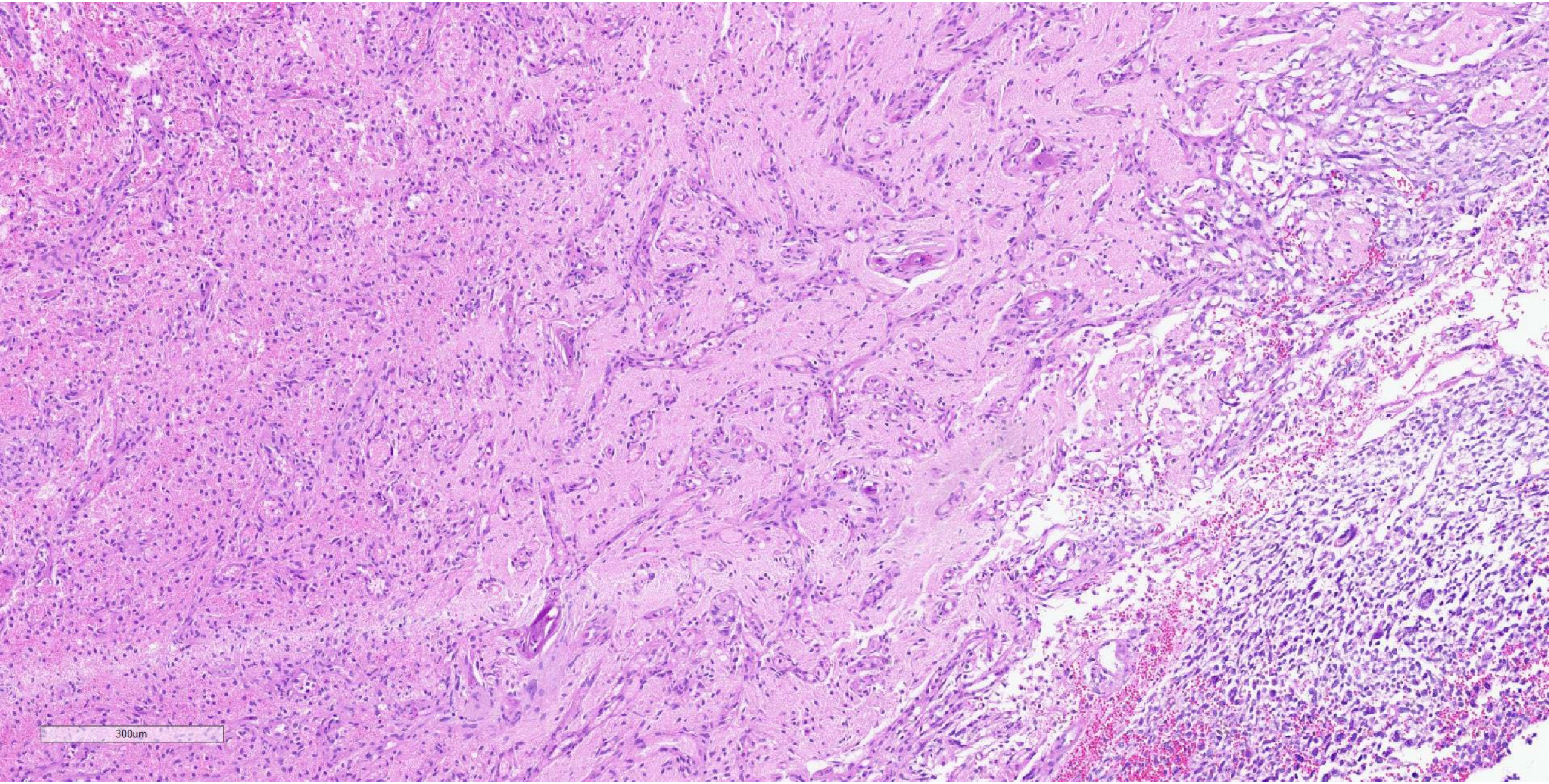
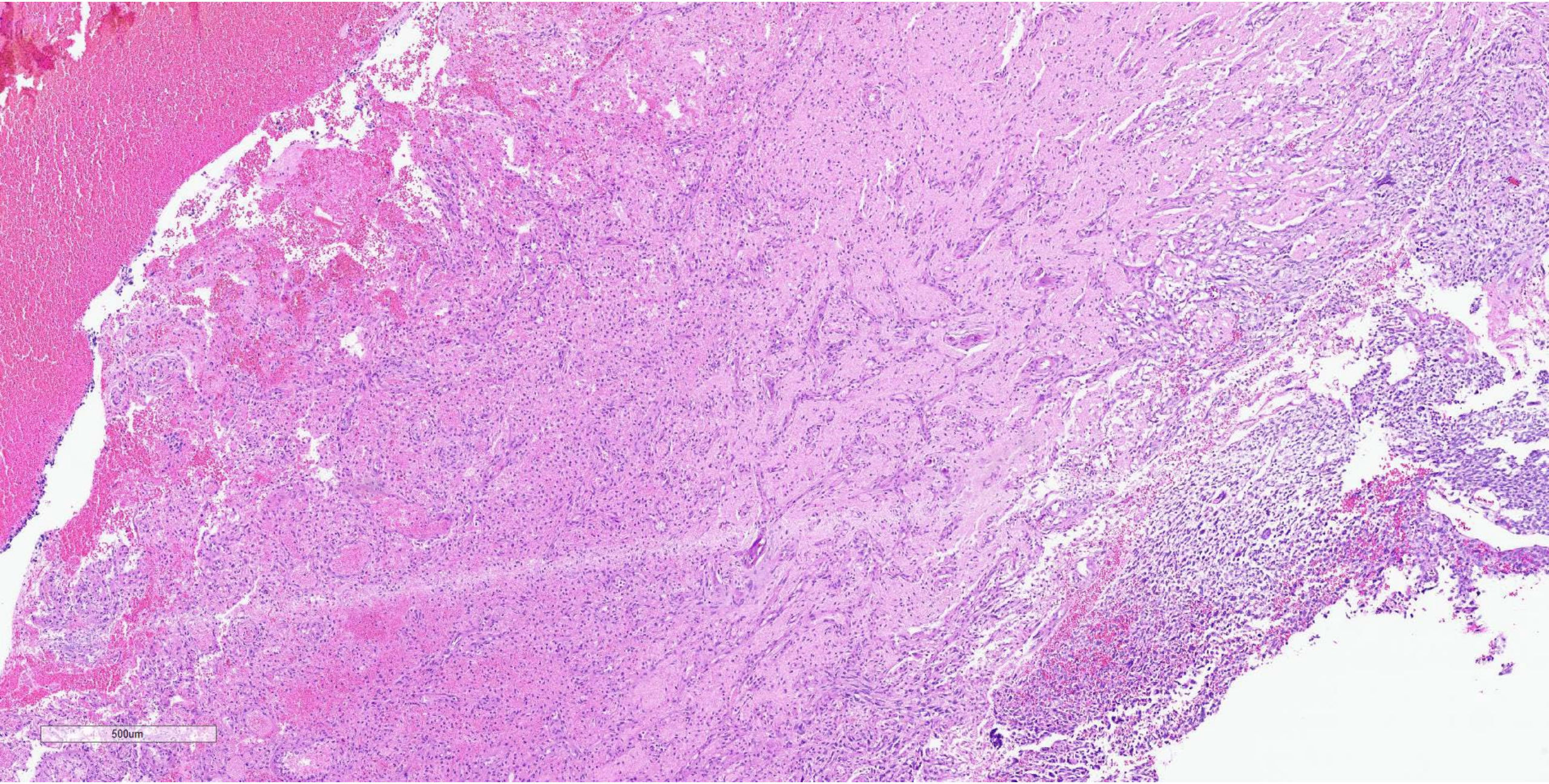

1mm


300um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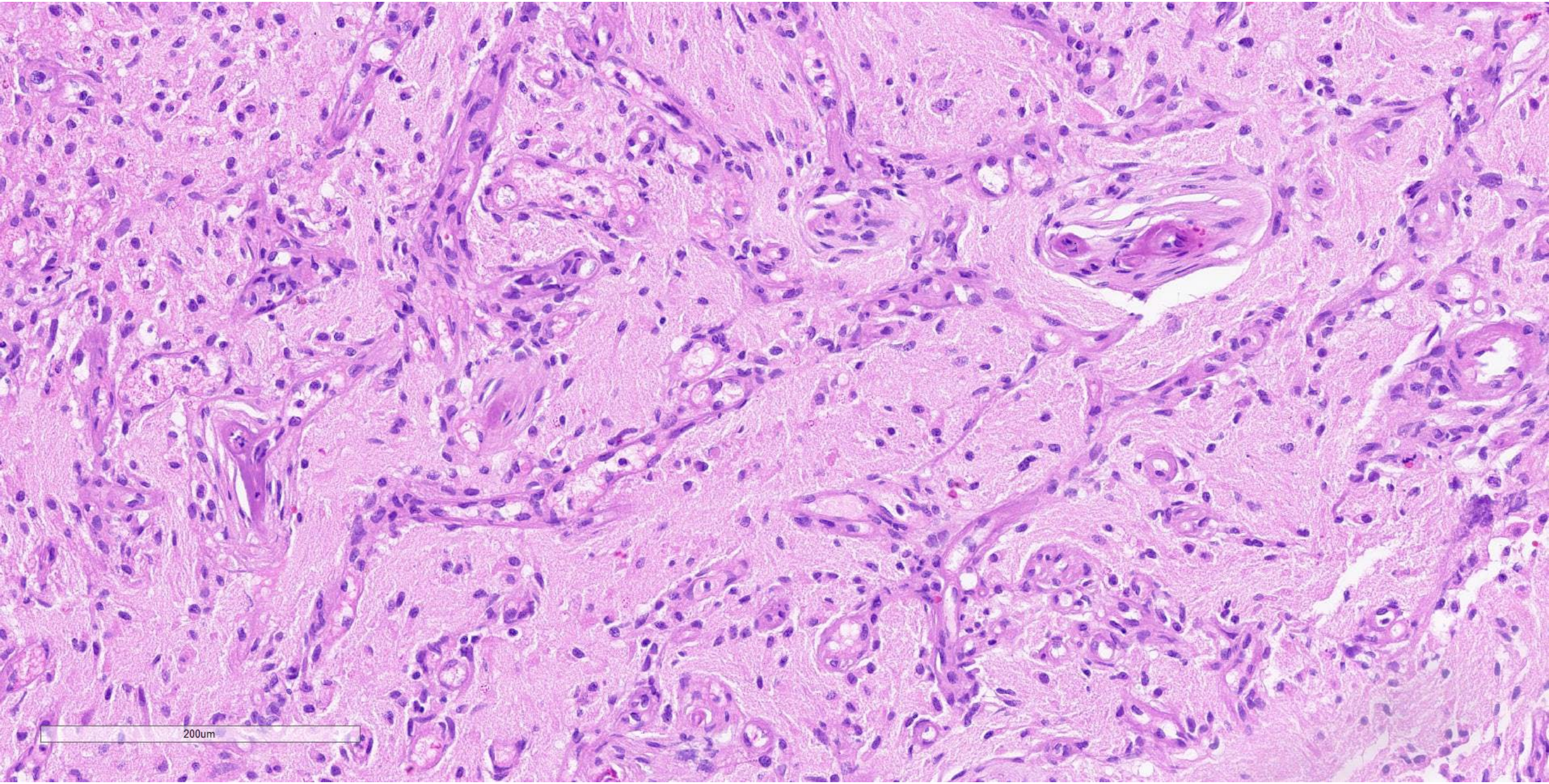
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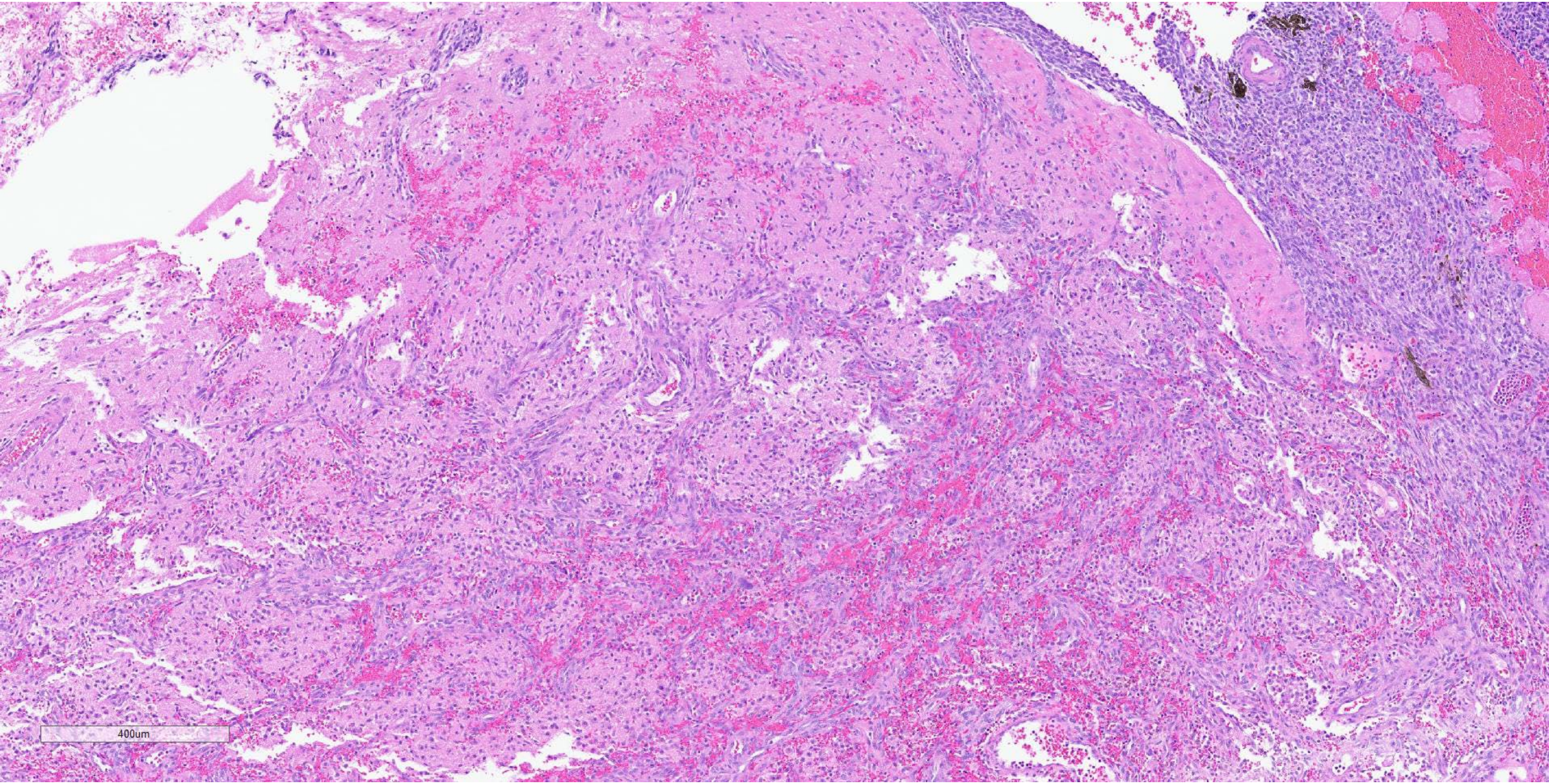
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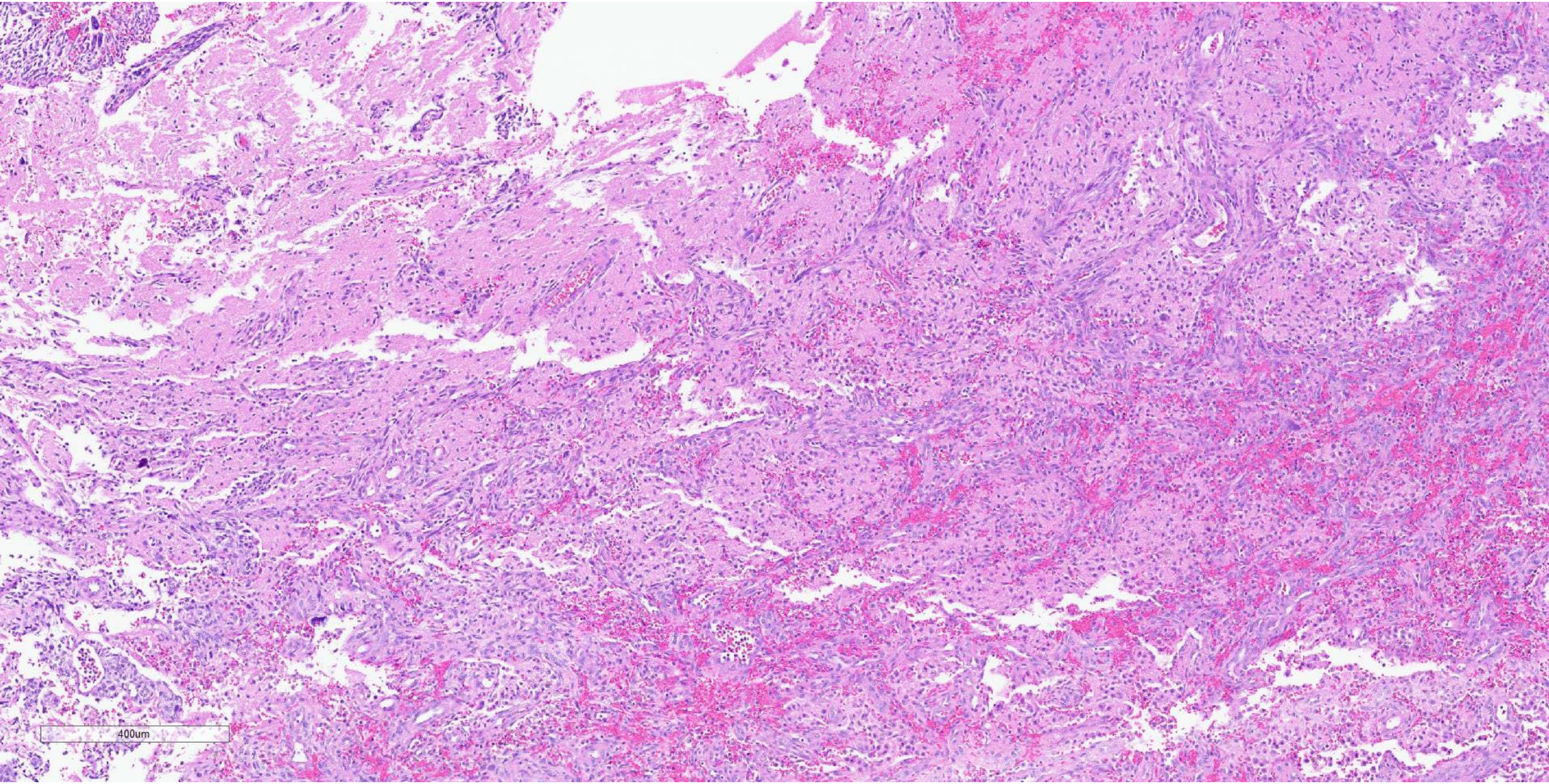
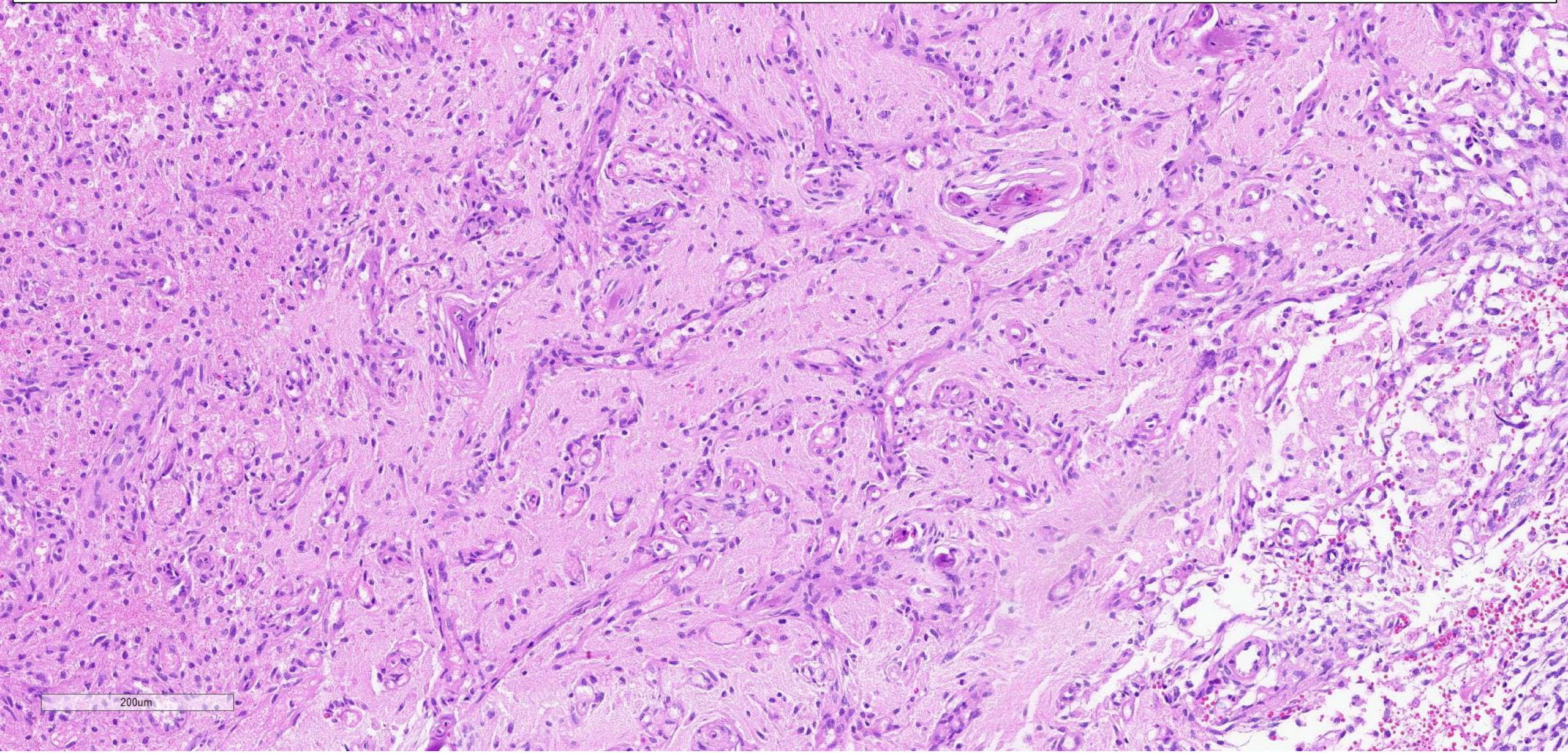
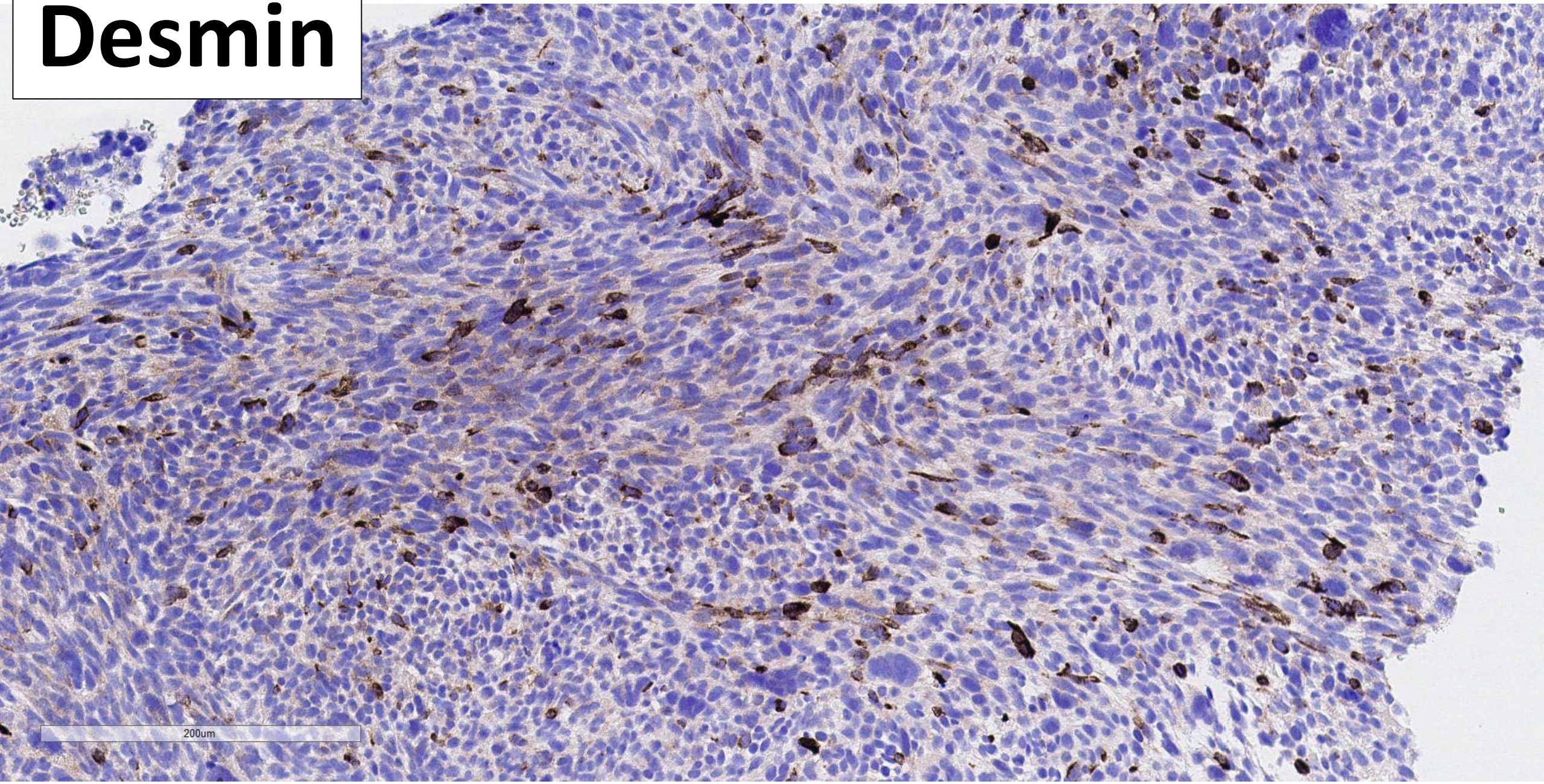

400um

Vascular Proliferation at the Tumor/Brain Interface in a Checkerboard Pattern



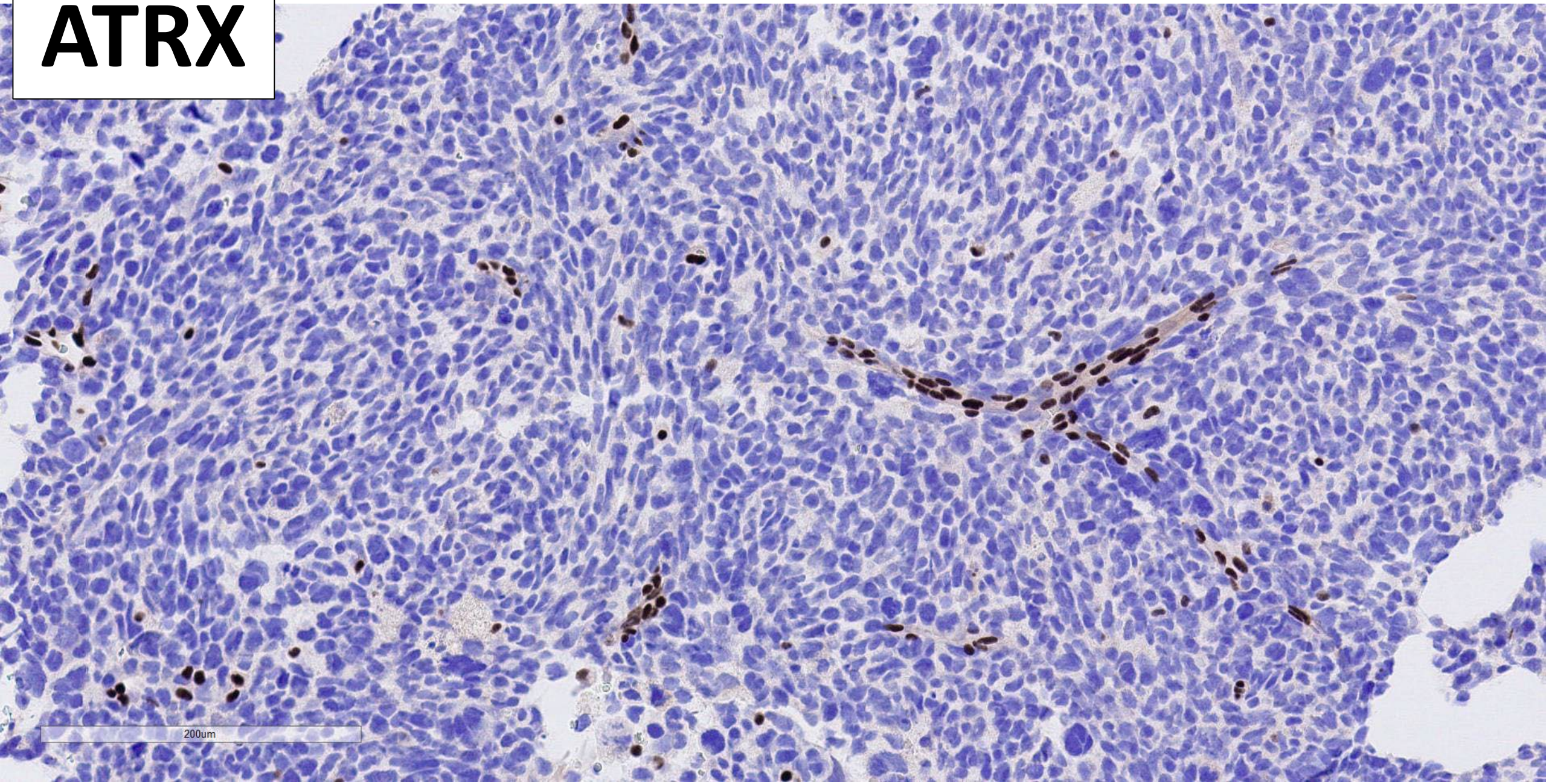
Differentiation Marker Immunophenotyping

Desmin

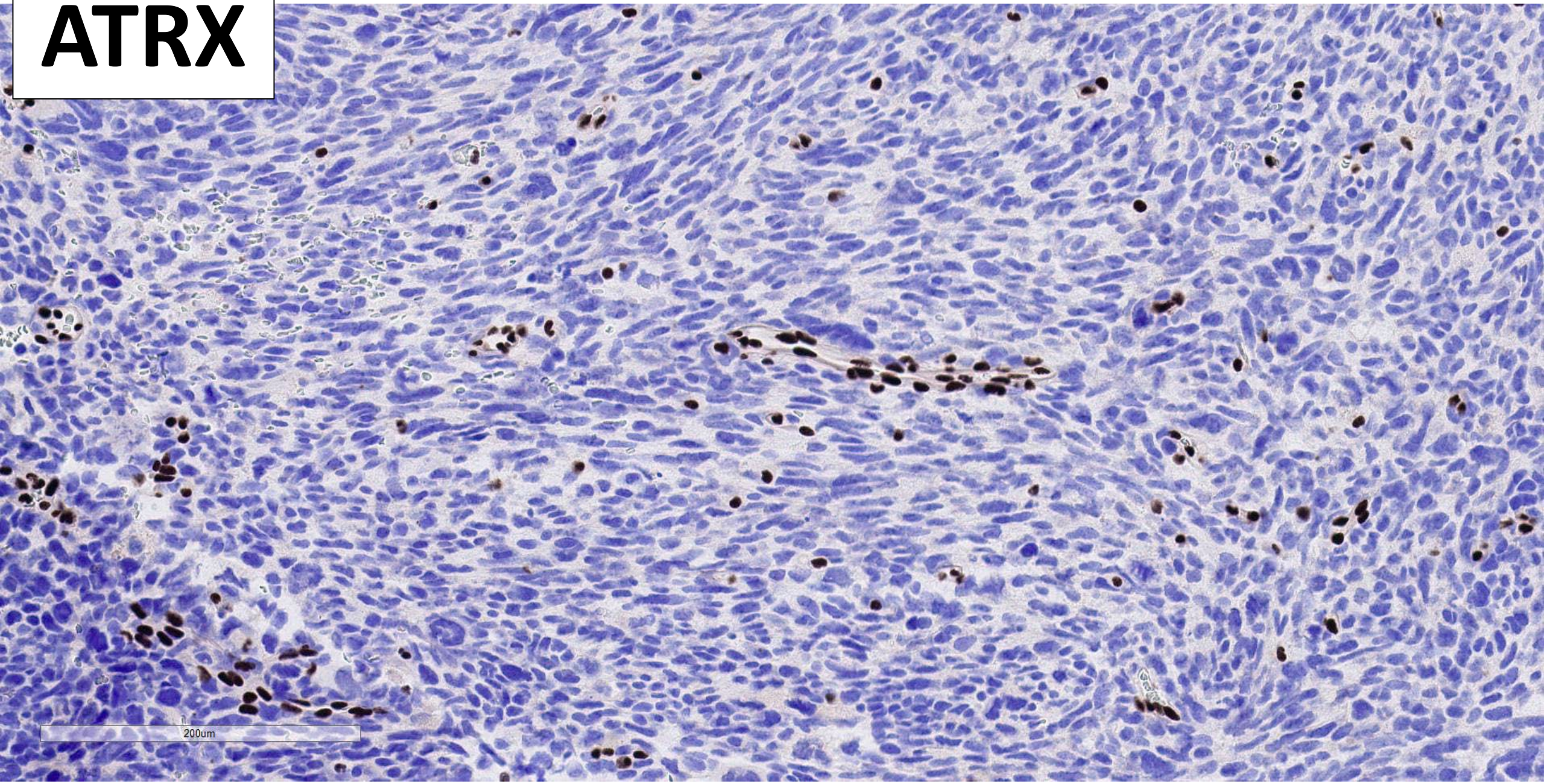


Molecular Signature Surrogate Immunophenotyping

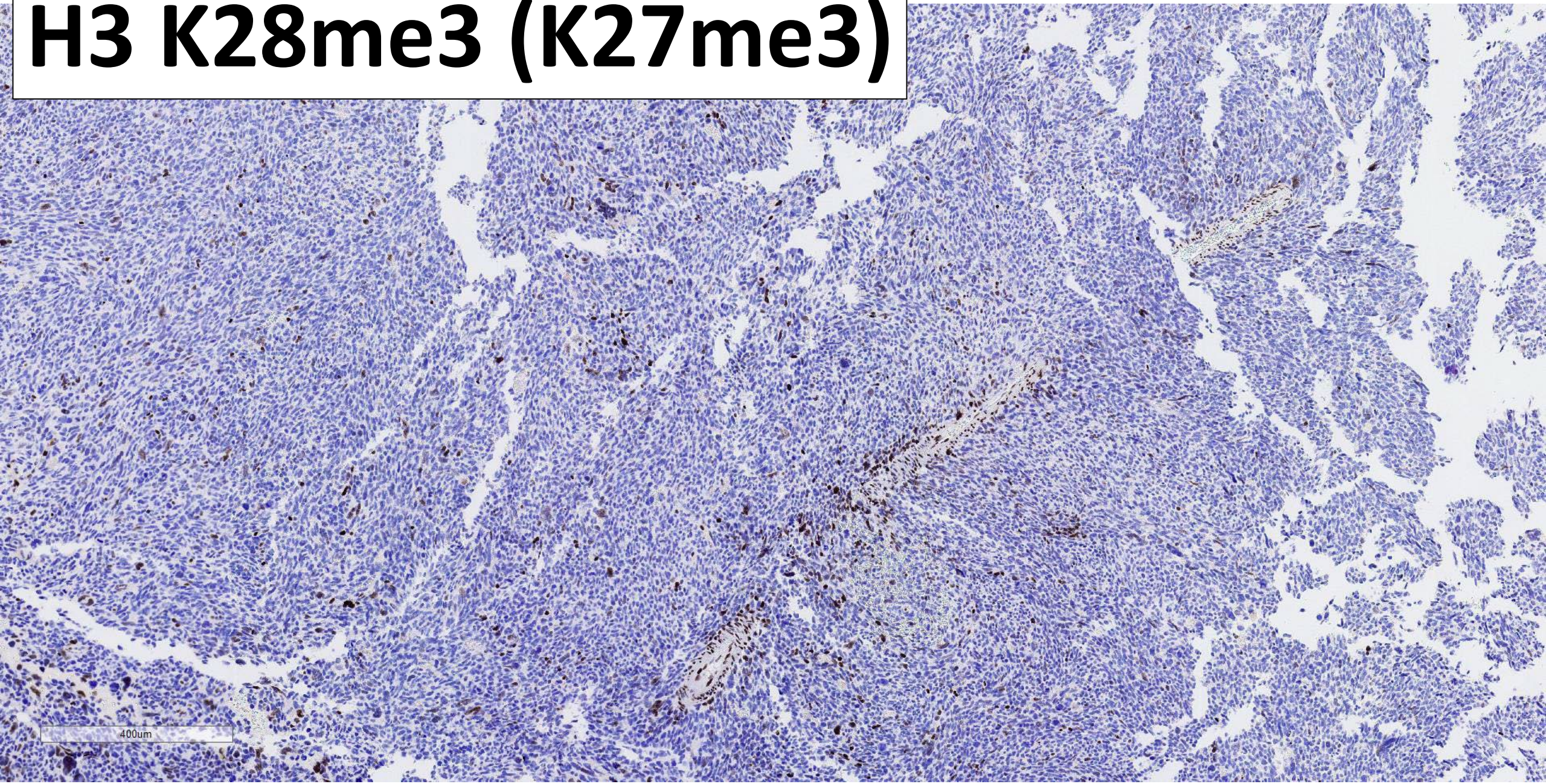
ATRX



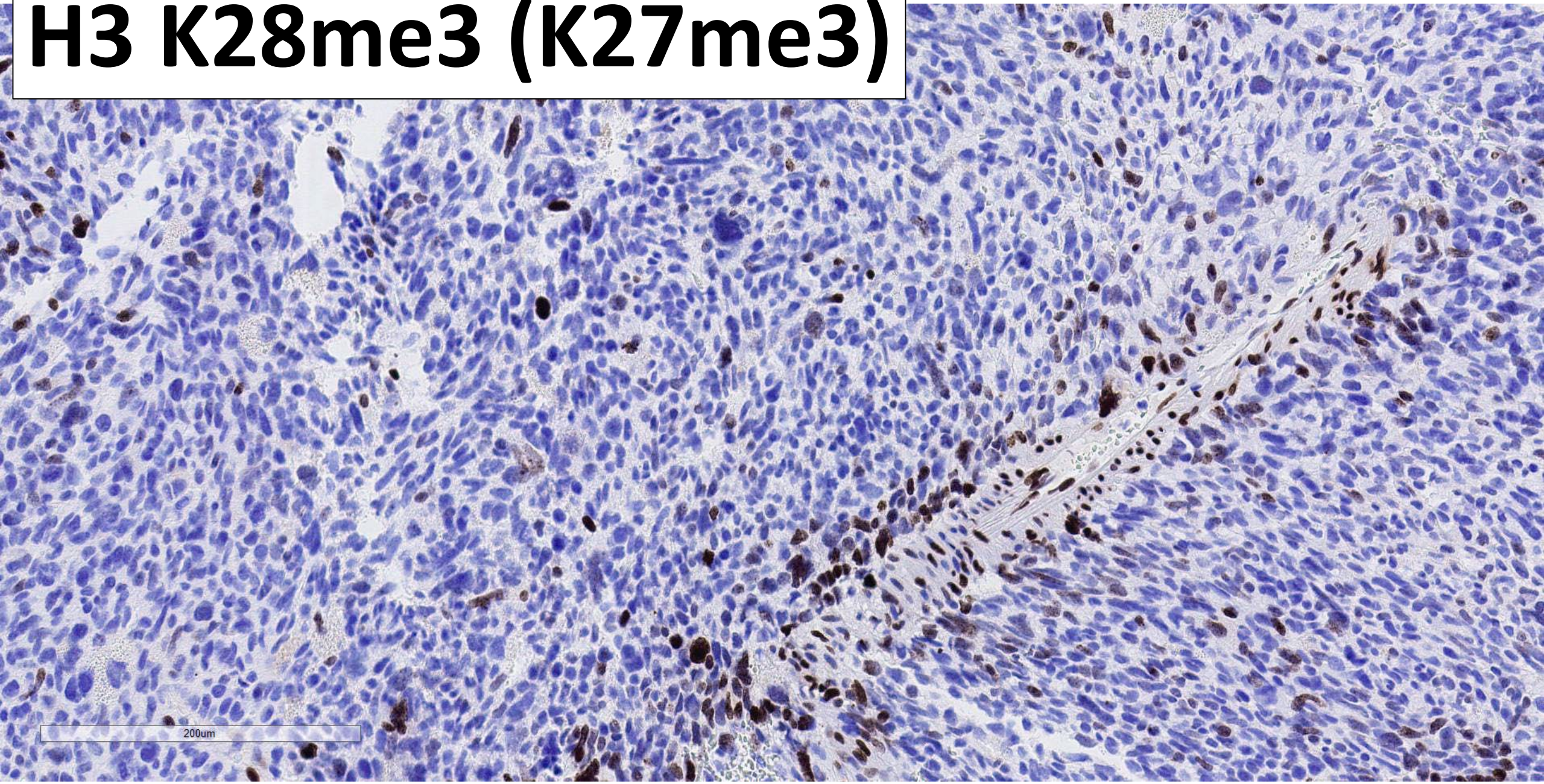
ATRX



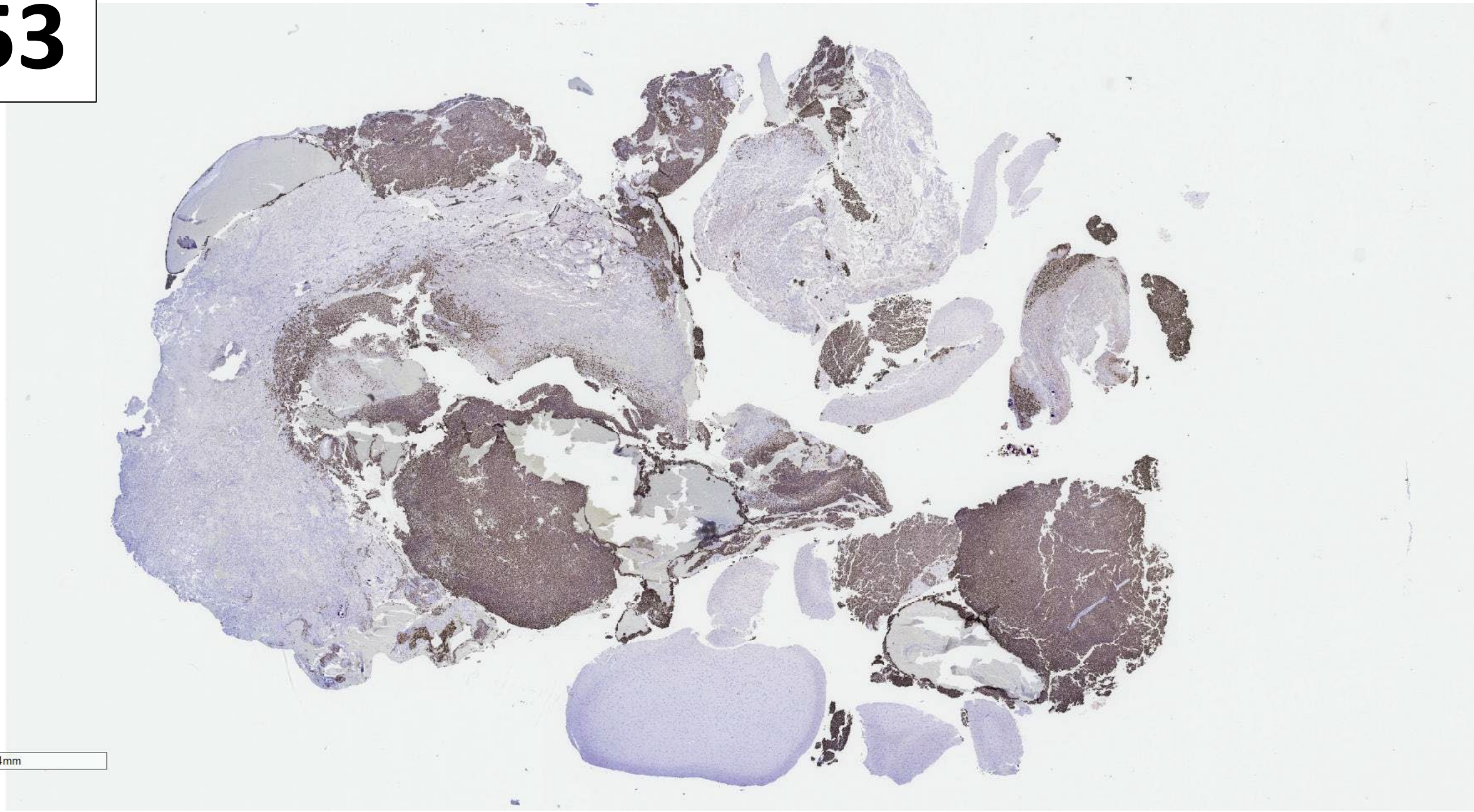
H3 K28me3 (K27me3)



H3 K28me3 (K27me3)



p53



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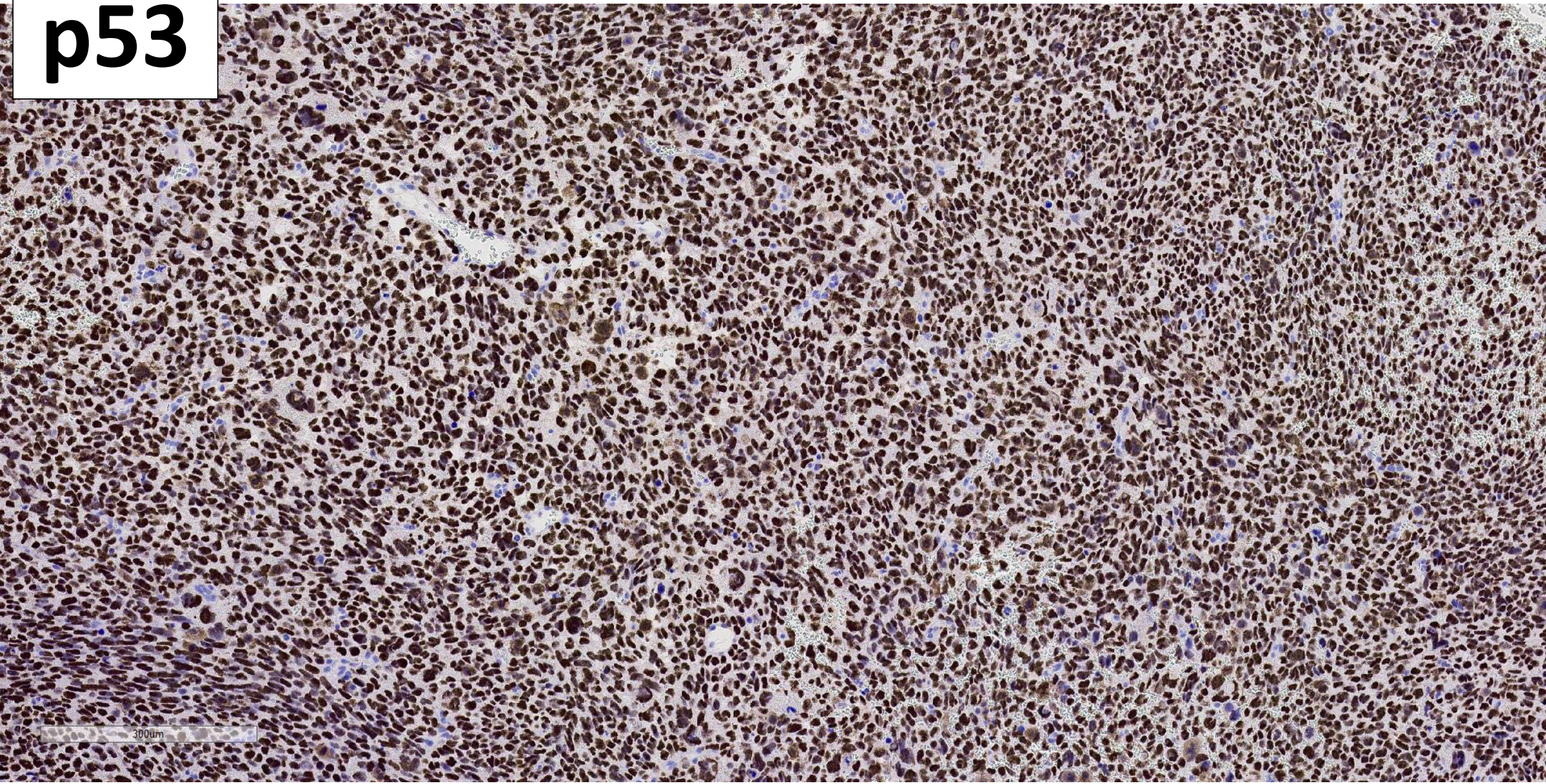
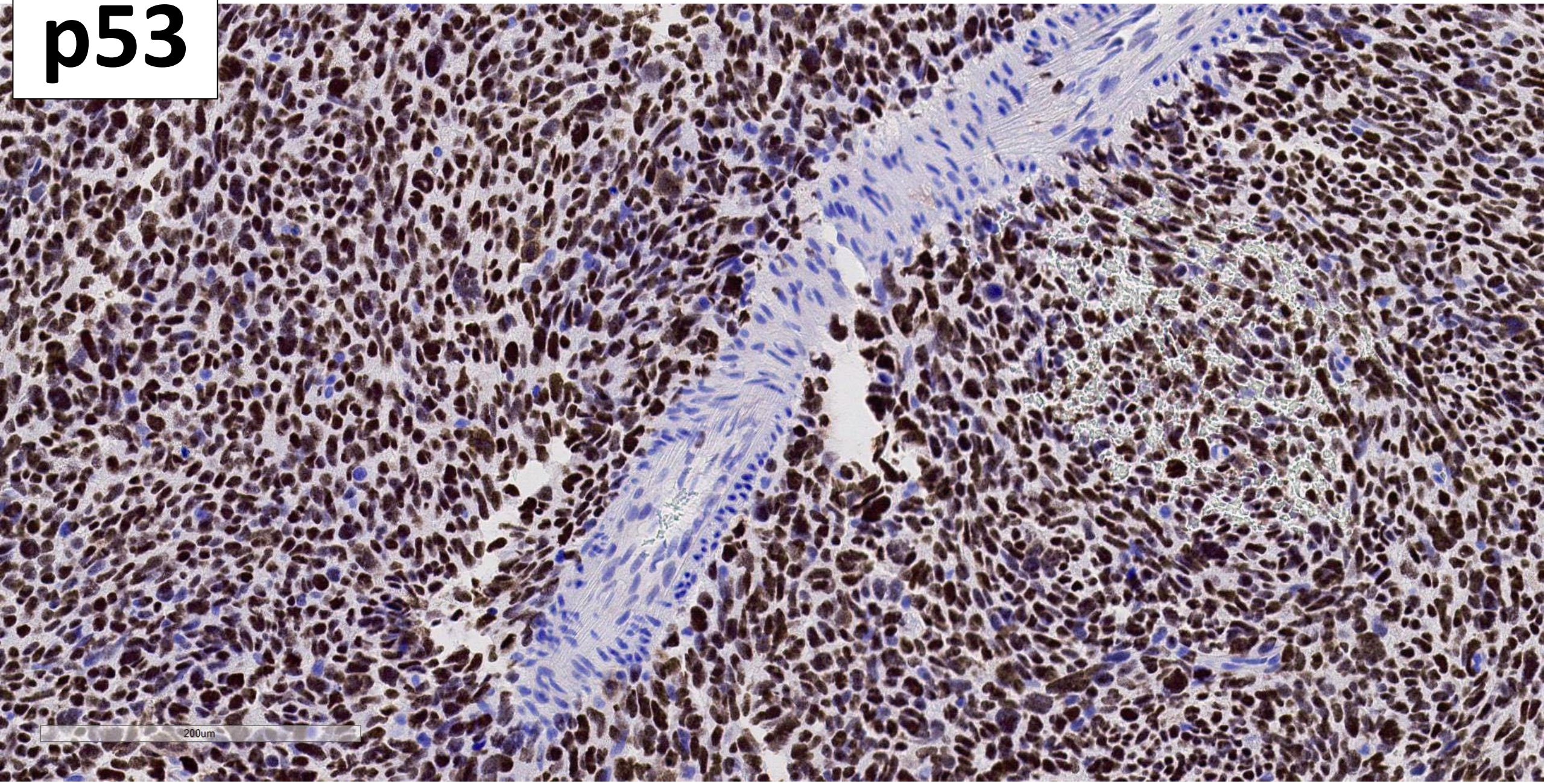
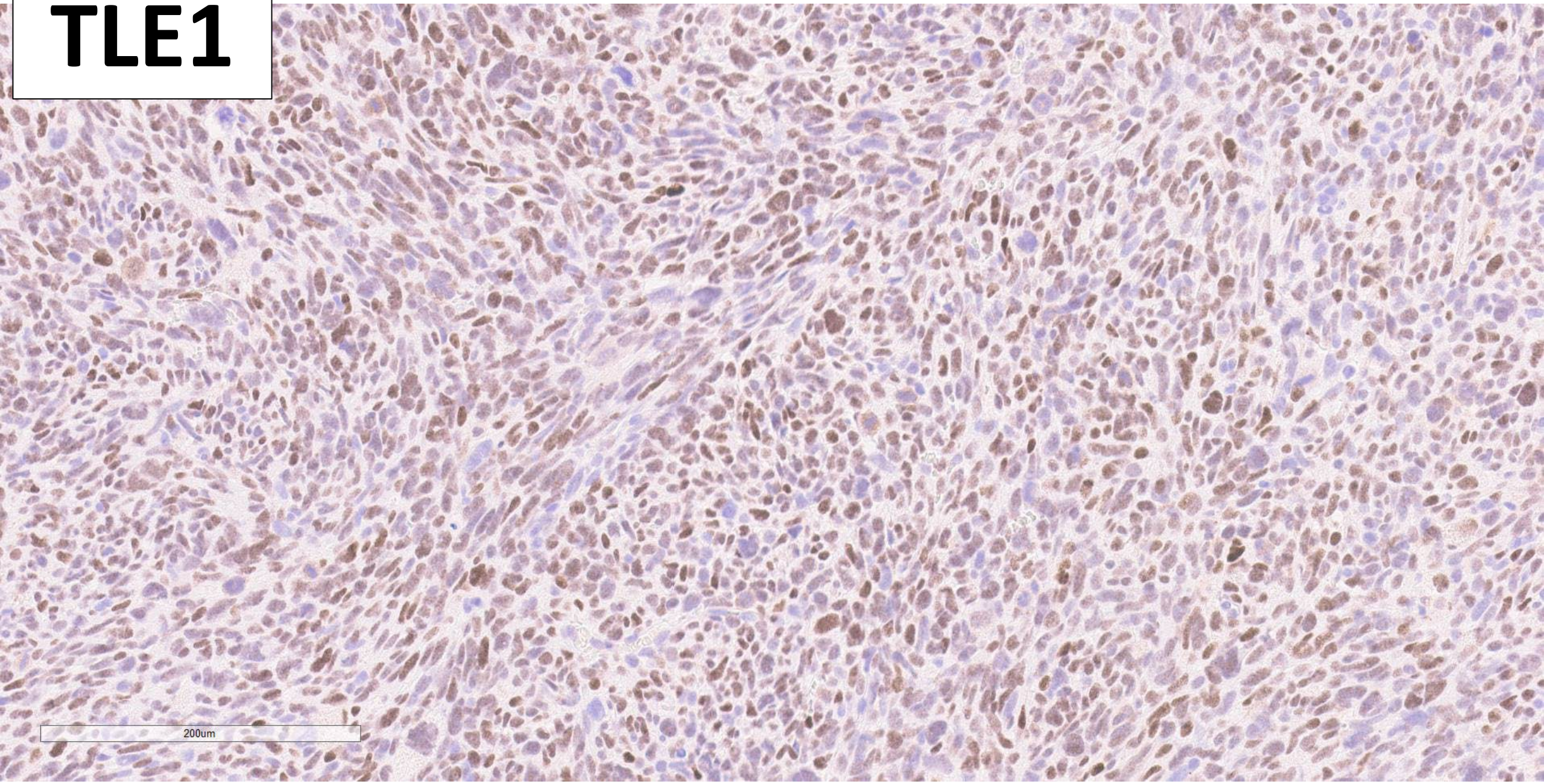


p53



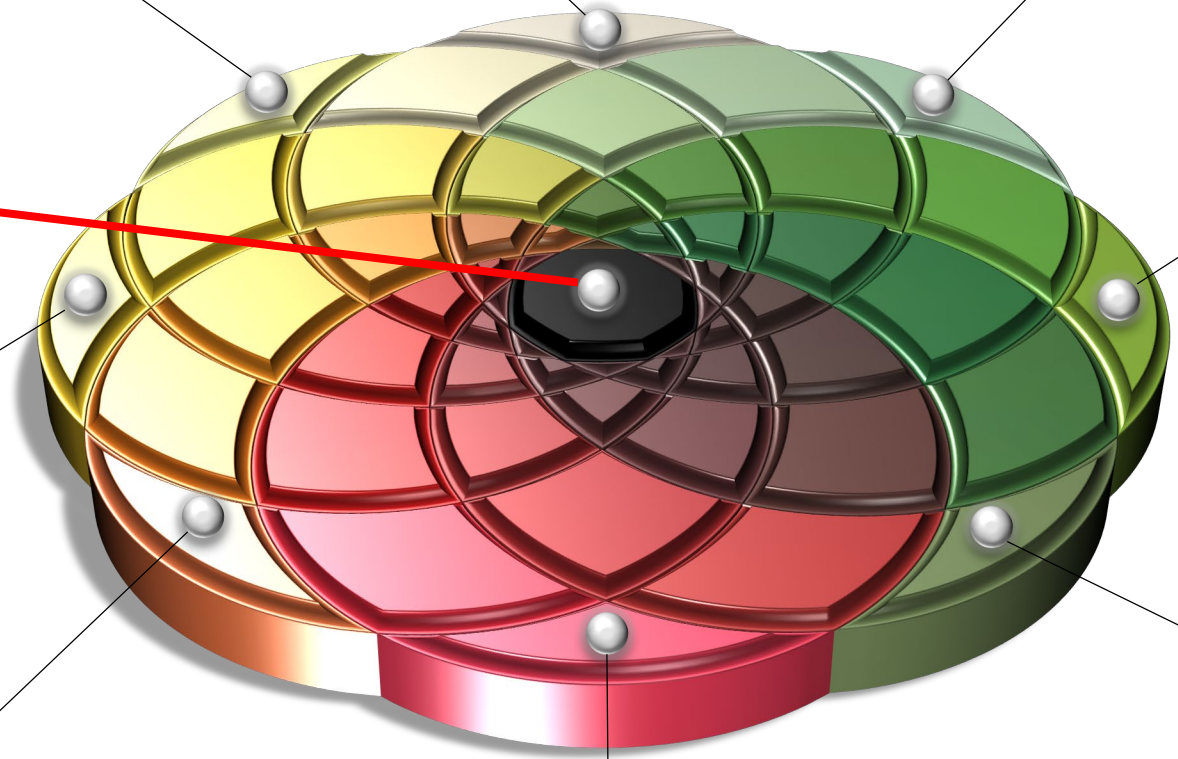
TLE1



Summary

- 5-year-old male
- Circumscribed hemorrhagic mass in the left frontal lobe
- Multiple bilateral supratentorial and infratentorial developmental venous anomalies (DVAs, "venous angiomas")
- Compact circumscribed spindle-cell tumor with highly elevated cell proliferation indices
- Bizarre giant cell component
- Scattered cells with conspicuous brightly-eosinophilic cytoplasmic droplets
- Patchy delicate reticulin deposition
- Organizing hemorrhage with hematoiden, hemosiderin, granulation tissue and macrophages
- Florid microvascular proliferation at the tumor/brain interface in a checkerboard pattern
- Patchy, but unequivocal, cytoplasmic desmin expression
- Strong diffuse nuclear p53 protein expression (indicative of a *TP53* mutation)
- Strong diffuse nuclear TLE1 expression

8-Data-Sphere Model for Oncologic Diagnosis



Age

Molecular Signature

Gender

Diagnosis

Clinical History

Differentiation
Phenotype

Morphology

Anatomic
Location

Imaging Characteristics

Where is the patient from?

PERU

DIAGNOSIS?

Diagnosis

Twelve H&E-stained outside slides and one FFPE block (redacted) from which special studies (reticulin, CD34, ERG, p53, desmin, ATRX, BRAF-V600E, H3 K27me3, TLE1, desmin, myogenin, myoD1, quantitative Ki67 antigen) were performed at MDACC, brain, left frontal lobe, craniotomy with resection:

HIGH-GRADE SPINDLE CELL SARCOMA WITH CHARACTERISTIC FEATURES OF PRIMARY INTRACRANIAL SARCOMA, *DICER1*-MUTANT

Diagnosis

Twelve H&E-stained outside slides and one FFPE block (redacted) from which special studies (reticulin, CD34, ERG, p53, desmin, ATRX, BRAF-V600E, H3 K27me3, TLE1, desmin, myogenin, myoD1, quantitative Ki67 antigen) were performed at MDACC, brain, left frontal lobe, craniotomy with resection:

HIGH-GRADE SPINDLE CELL SARCOMA WITH CHARACTERISTIC FEATURES OF PRIMARY INTRACRANIAL SARCOMA, *DICER1*-MUTANT
CNS WHO GRADE 4

Diagnosis

Twelve H&E-stained outside slides and one FFPE block (redacted) from which special studies (reticulin, CD34, ERG, p53, desmin, ATRX, BRAF-V600E, H3 K27me3, TLE1, desmin, myogenin, myoD1, quantitative Ki67 antigen) were performed at MDACC, brain, left frontal lobe, craniotomy with resection:

HIGH-GRADE SPINDLE CELL SARCOMA WITH CHARACTERISTIC FEATURES OF PRIMARY INTRACRANIAL SARCOMA, *DICER1*-MUTANT
CNS WHO GRADE 4

(SEE COMMENT)

Electronically signed by Gregory N. Fuller, MD

Comment

H&E-stained sections show a high-grade spindle cell neoplasm with characteristic morphologic features of **Primary Intracranial Sarcoma, *DICER1*-Mutant**. The features include spindle cell morphology, highly-elevated cell proliferation (quantitative Ki67 antigen index to be reported in an Addendum), scattered pleomorphic giant cells, scattered cells with highly-characteristic intracytoplasmic eosinophilic droplets, intratumoral hemorrhage with organizing hematoma and hemosiderin deposition, and florid microvascular proliferation in a "checkerboard" pattern at the interface with the surrounding brain parenchyma (the latter feature is well-described in *DICER1*-mutant intracranial sarcoma; see ref 3 below). Reticulin staining shows focal delicate deposition.

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Desmin: POSITIVE (focal strong cytoplasmic expression in a cohort of tumor cells)
ATRX: LOSS of nuclear expression in tumor cells
H3 K27me3: LOSS of the trimethylation mark in a major cohort of tumor cells

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MyoD1: Negative
Myogenin: Negative
BRAF-V600E: Negative
ERG: Highlights prominent vasculature, including tumor/brain interface microvascular proliferation
CD34: Highlights prominent vasculature, including tumor/brain interface microvascular proliferation; Negative in tumor cells

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As noted above, confirmatory MDA MAPP NGS is underway.

References

1. Diaz Coronado DY et al. Primary central nervous system sarcoma with DICER1 mutation-treatment results of a novel molecular entity in pediatric Peruvian patients. Cancer 2021 [PMID 34674226]
2. Alexandrescu S et al. Loss of histone H3 trimethylation on lysine 27 and nuclear expression of transducin-like enhancer 1 in primary intracranial sarcoma, DICER1-mutant. Histopathology 2021 [PMID 32692439]
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MDA MAPP: Mutation Analysis Precision Panel Final Report

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SNVs/Indels | CNVs | Fusions | TMB | MSI

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SNVs/Indels	CNVs	Fusions	TMB	MSI
More than 5 genes. See details	*None*	*None*	17 mut/Mb	Stable (MSS)

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Somatic Mutations (SNVs/Indels)

Gene	DNA	Protein	Location	VAF	Type
ARID1B	c.6778G>A	p.G2260S	Exon 20	35%	SNV - Missense
ARID2	c.4984G>A	p.V1662I	Exon 17	35%	SNV - Missense
BCR	c.2116-1G>A	p.?	Splice? (Intron 8)	45%	Splice? - Unknown
CREBBP	c.6995G>A	p.G2332D	Exon 31	34%	SNV - Missense

Somatic Mutations (SNVs/Indels)

Gene	DNA	Protein	Location	VAF	Type
CUL4B	c.2440G>A	p.?	Splice? (Exon 19)	67%	SNV - Unknown
DICER1	c.5428G>T	p.D1810Y	Exon 27	52%	SNV - Missense
DICER1	c.904-1G>A	p.?	Splice? (Intron 9)	27%	Splice? - Unknown

HDAC9	c.577C>T	p.P193S	Exon 5	35%	SNV - Missense
HOXB13	c.271C>T	p.R91*	Exon 1	36%	SNV - Nonsense
KDR	c.2524C>T	p.R842C	Exon 18	5%	SNV - Missense
KEL	c.874C>T	p.R292W	Exon 8	37%	SNV - Missense
KMT2D	c.3613G>A	p.V1205I	Exon 11	30%	SNV - Missense
KMT2D	c.4473G>A	p.W1491*	Exon 16	36%	SNV - Nonsense
KRAS	c.35G>A	p.G12D	Exon 2	58%	SNV - Missense
MLH3	c.901G>A	p.E301K	Exon 2	35%	SNV - Missense
MST1	c.357C>T	p.?	Splice? (Exon 4)	35%	SNV - Unknown
NOTCH4	c.2791G>A	p.V931M	Exon 18	31%	SNV - Missense
NRAS	c.35G>A	p.G12D	Exon 2	36%	SNV - Missense
PAK5	c.1723C>T	p.L575F	Exon 7	50%	SNV - Missense
PARPBP	c.1528A>G	p.R510G	Exon 11	34%	SNV - Missense
PIM1	c.218G>A	p.R73Q	Exon 3	38%	SNV - Missense
PRKDC	c.125G>A	p.C42Y	Exon 1	37%	SNV - Missense
PTPRB	c.5798G>T	p.R1933L	Exon 27	37%	SNV - Missense
ROS1	c.6160G>T	p.V2054F	Exon 39	37%	SNV - Missense
RPTOR	c.3615G>A	p.M1205I	Exon 31	32%	SNV - Missense
SETD2	c.1930G>A	p.D644N	Exon 3	30%	SNV - Missense
TP53	c.841G>A	p.D281N	Exon 8	57%	SNV - Missense
ZFHX3	c.9634C>T	p.P3212S	Exon 10	7%	SNV - Missense

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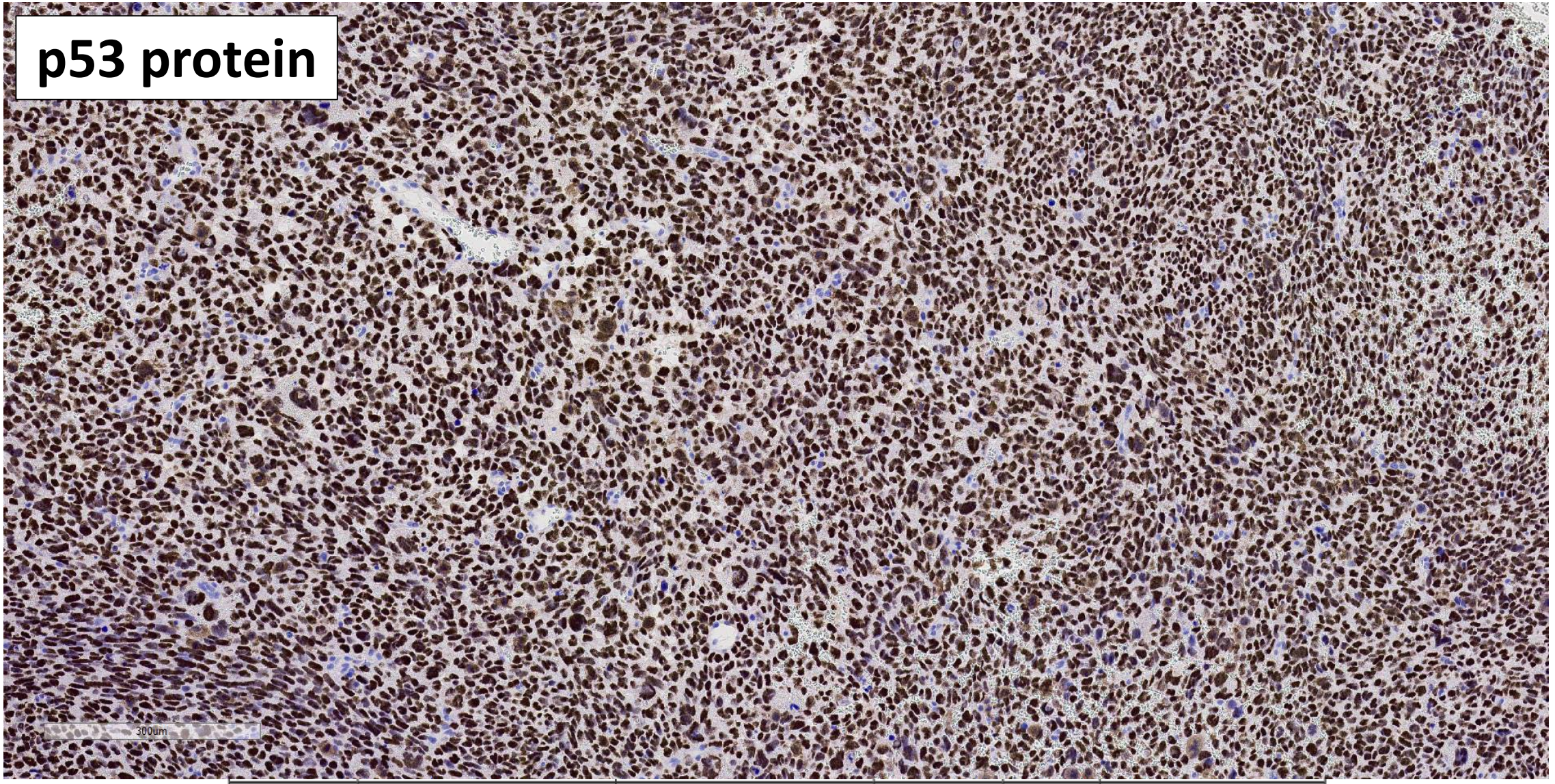
TP53



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CANCER 2021 PMID 34674226

Primary Central Nervous System Sarcoma With *DICER1* Mutation—Treatment Results of a Novel Molecular Entity in Pediatric Peruvian Patients

Rosdali Y. Diaz Coronado, MD [1,2]; Martin Mynarek, MD[3]; Christian Koelsche, MD[4]; Pamela Mora Alferez, MD[5]; Sandro Casavilca Zambrano, MD[6]; Antonio Wachtel Aptowitzer, MD[7]; Felix Sahm, MD[8,9]; Andreas von Deimling, MD[8,9] Ulrich Schüller, MD[3,10,11]; Michael Spohn, MSc[10,12]; Dominik Sturm, MD[13,14,15]; Stefan M. Pfister, MD[13,14,16]; Andres Morales La Madrid, MD[17]; Raymundo Sernaque Quintana, MD[18]; Gustavo Sarria Bardales, MD[2,19]; Tatiana Negreiros Chinchihuara, MD[19]; Luis Ojeda Medina, MD[20]; Pamela Garcia-Corrochano Medina, MD[20]; Danny A. Campos Sanchez, MD[21]; Jimena Ponce Farfan, MD[7]; Stefan Rutkowski, MD[3]; and Juan L. Garcia Leon, MD[1,2,7]

Histopathology 2021

Histopathology 2021, 78, 265–275 PMID 32692439

Loss of histone H3 trimethylation on lysine 27 and nuclear expression of transducin-like enhancer 1 in primary intracranial sarcoma, *DICER1*-mutant

Sanda Alexandrescu,[1] David M Meredith,[2] Hart G Lidov,[1] Rita Alaggio,[3] Mariangela Novello,[4] Keith L Ligon[2] & Sara O Vargas[1]

[1]*Department of Pathology, Boston Children's Hospital, Boston, MA,* [2]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA,* [3]*Department of Pathology, Bambino Gesu Hospital, Rome, and* [4]*Department of Pathology, San Bartolo Hospital, Vicenza, Italy*

Modern Pathology (2020)
PMID 32291395

ARTICLE

DICER1-associated central nervous system sarcoma in children: comprehensive clinicopathologic and genetic analysis of a newly described rare tumor

Junne Kamihara[1] · Vera Paulson[2,13] · Micheál A. Breen[3] · Theodore W. Laetsch[4] · Dinesh Rakheja[5] · David S. Shulman[1] · Michelle L. Schoettler[1] · Catherine M. Clinton[6] · Abigail Ward[6] · Deirdre Reidy[6] · R. Seth Pinches[7] · Daniel A. Weiser[8] · Elizabeth A. Mullen[1] · Jaclyn Schienda[6] · Paul A. Meyers[9] · Steven G. DuBois[1] · Jonathan A. Nowak[10] · William D. Foulkes[11] · Kris Ann P. Schultz[12] · Katherine A. Janeway[1] · Sara O. Vargas[2] · Alanna J. Church[2]

Acta Neuropathol. 2019 **PMID 30649606**

Primary intracranial sarcomas with *DICER1* mutation often contain prominent eosinophilic cytoplasmic globules and can occur in the setting of neurofibromatosis type 1

Julieann C. Lee[1], Javier E. Villanueva-Meyer[2], Sean P. Ferris[1], Emily A. Sloan[1], Jeffrey W. Hofmann[1], Eyas M. Hattab[3], Brian J. Williams[4], Hua Guo[5], Joseph Torkildson[6], Adriana Florez[7], Jessica Van Ziffle[1,8], Courtney Onodera[1,8], James P. Grenert[1,8], Soo-Jin Cho[1], Andrew E. Horvai[1], David T.W. Jones[9,10], Stefan M. Pfister[9,11,12], Christian Koelsche[13,14], Andreas von Deimling[14,15], Andrey Korshunov[14,15], Arie Perry[1,16], and David A. Solomon

Pediatric Radiology (2019)
PMID 31620849

PEDIATRIC ONCOLOGIC IMAGING

Imaging of DICER1 syndrome

R. Paul Guillerman[1] · William D. Foulkes[2] · John R. Priest[3]

Acta Neuropathologica (2021)
PMID 34677675

CORRESPONDENCE

DICER1 syndrome in a young adult with pituitary blastoma

Anne-Sophie Chong[1,2] · HyeRim Han[3] · Steffen Albrecht[4] · Young Cheol Weon[5] · Sang Kyu Park[6] · William D. Foulkes[1,2,7,8]

Received: 20 September 2021 / Revised: 14 October 2021 / Accepted: 15 October 2021 / Published online: 22 October 2021

Acta Neuropathologica (2020)
PMID 30953130

REVIEW

An update on the central nervous system manifestations of DICER1 syndrome

Leanne de Kock[1,2] · John R. Priest[3] · William D. Foulkes[1,2,4] · Sanda Alexandrescu[5]

Modern Pathology 2021 PMID: 34599283

REVIEW ARTICLE

DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma

Iván A. González[1], Douglas R. Stewart[2], Kris Ann P. Schultz[3,4], Amanda P. Field[5], D. Ashley Hill[3,5,6] and Louis P. Dehner[3,7]✉

8 Data Sphere Model for Oncologic Diagnosis

Age

Molecular Signature

Gender

Diagnosis

Clinical History

Differentiation Markers

Morphology

Anatomic Location

Imaging Characteristics

There has never been a more exciting time to be working in the field of

Neuro-Oncologic Diagnostic Medicine!

Thank You!