AANP Diagnostic Slide Session Case 5

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Disclosures:

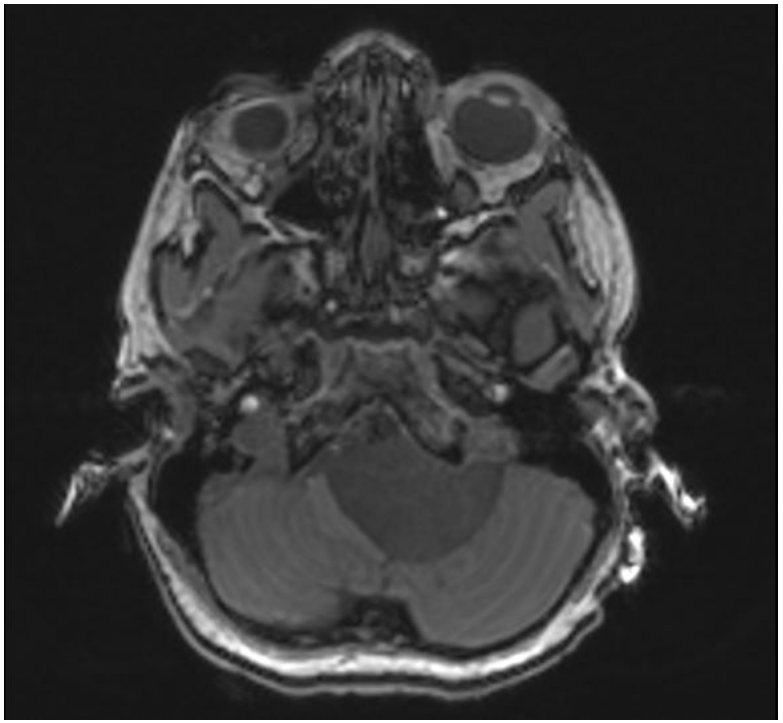
- No relevant disclosures to this presentation.

- No photography, please.

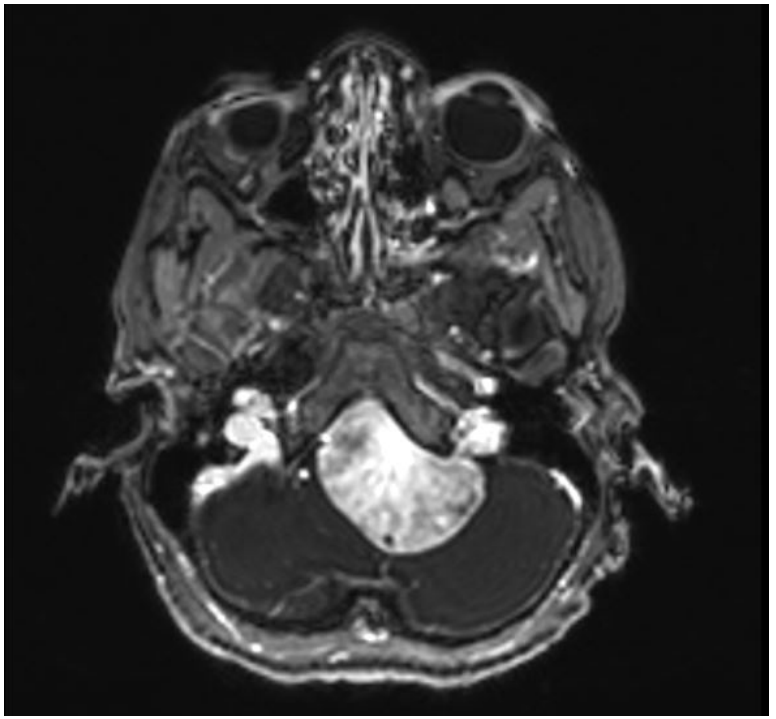
Brief Clinical History:

- **6-year-old male** with a two week history of headaches with recent nausea and vomiting
- Diagnosed strep throat, and treated with antibiotics without improvement
- While getting additional labs drawn, the patient had acute onset of **left sided facial drooping**, and was brought to the ER

MRI Findings:

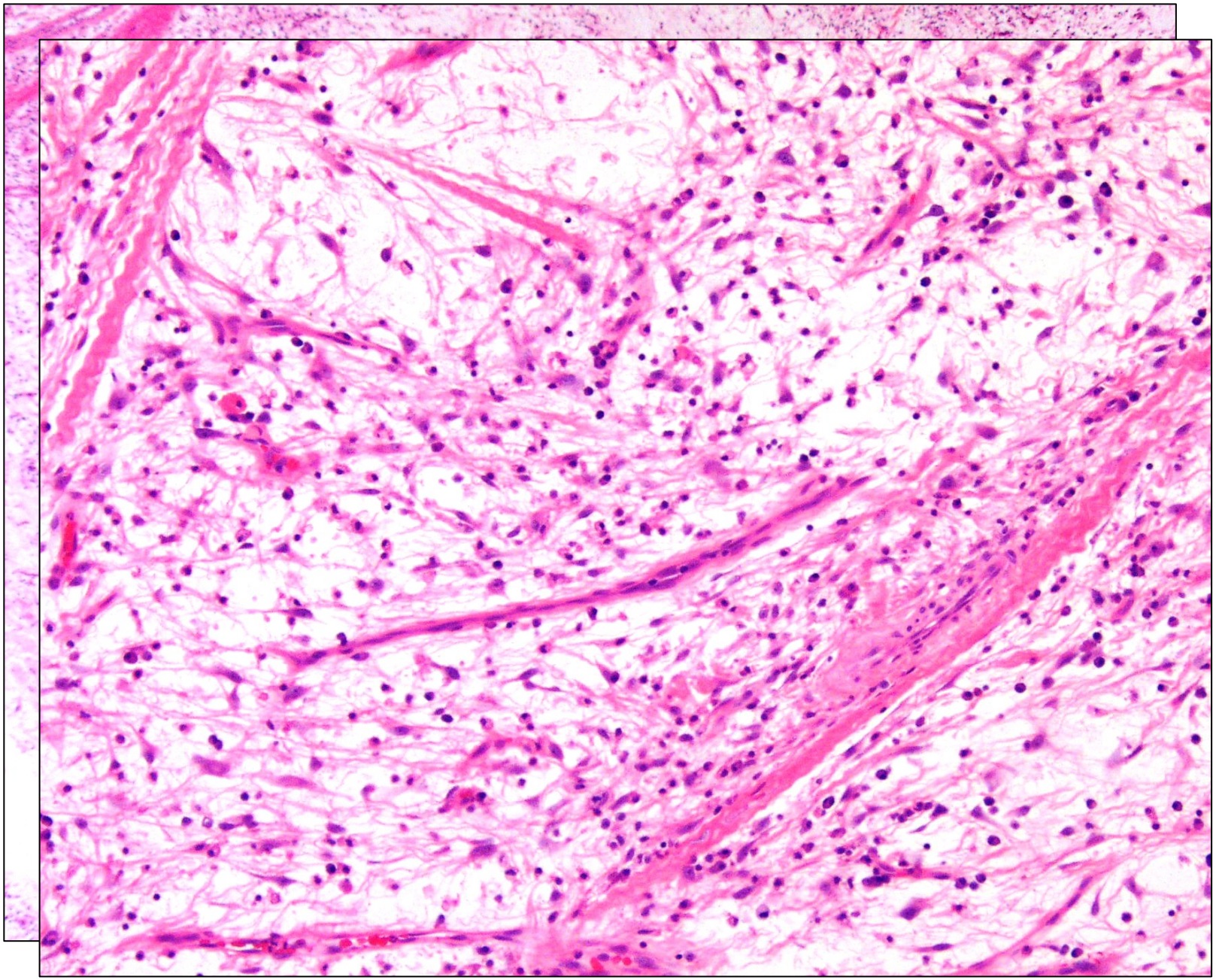


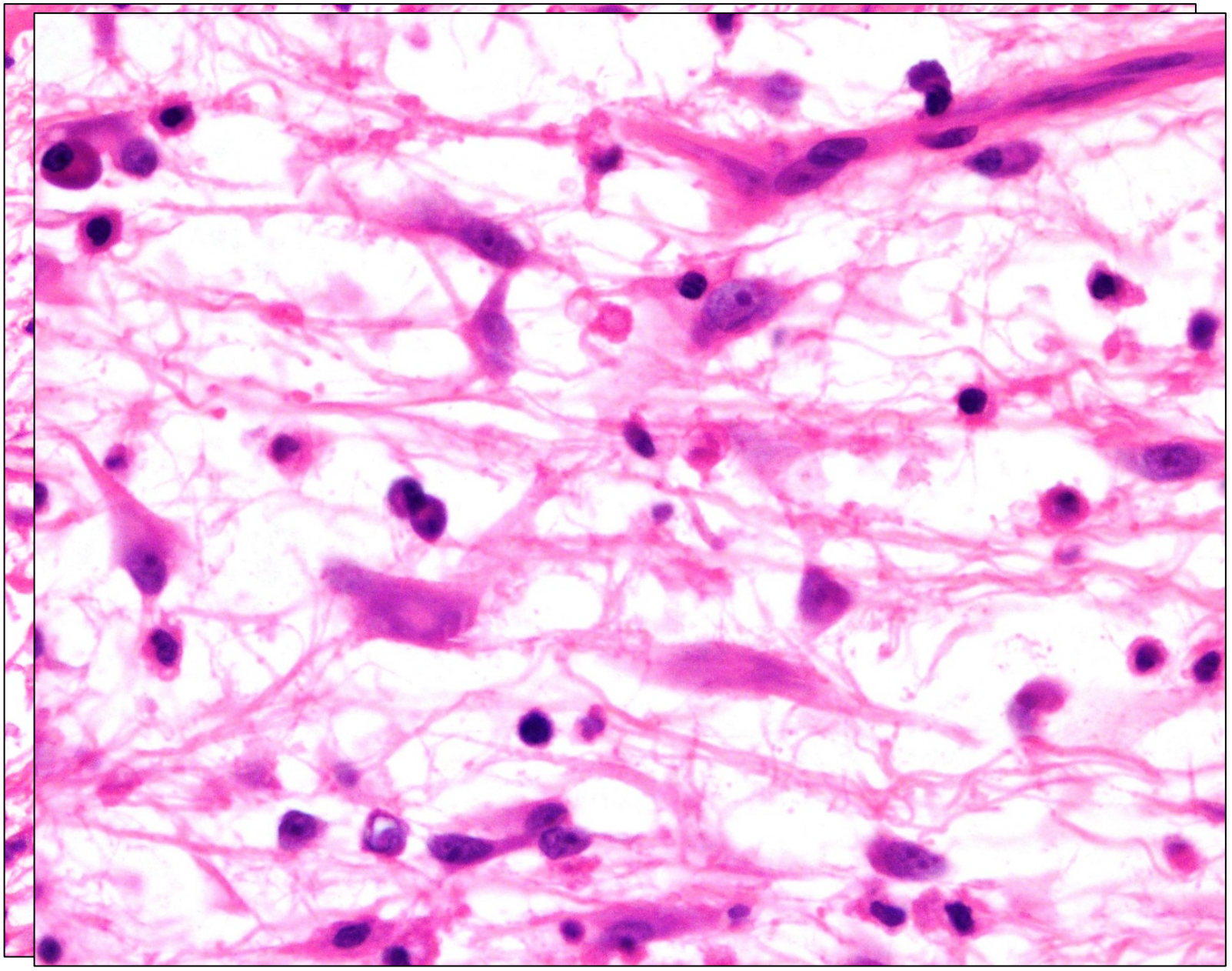
T1 Axial Pre

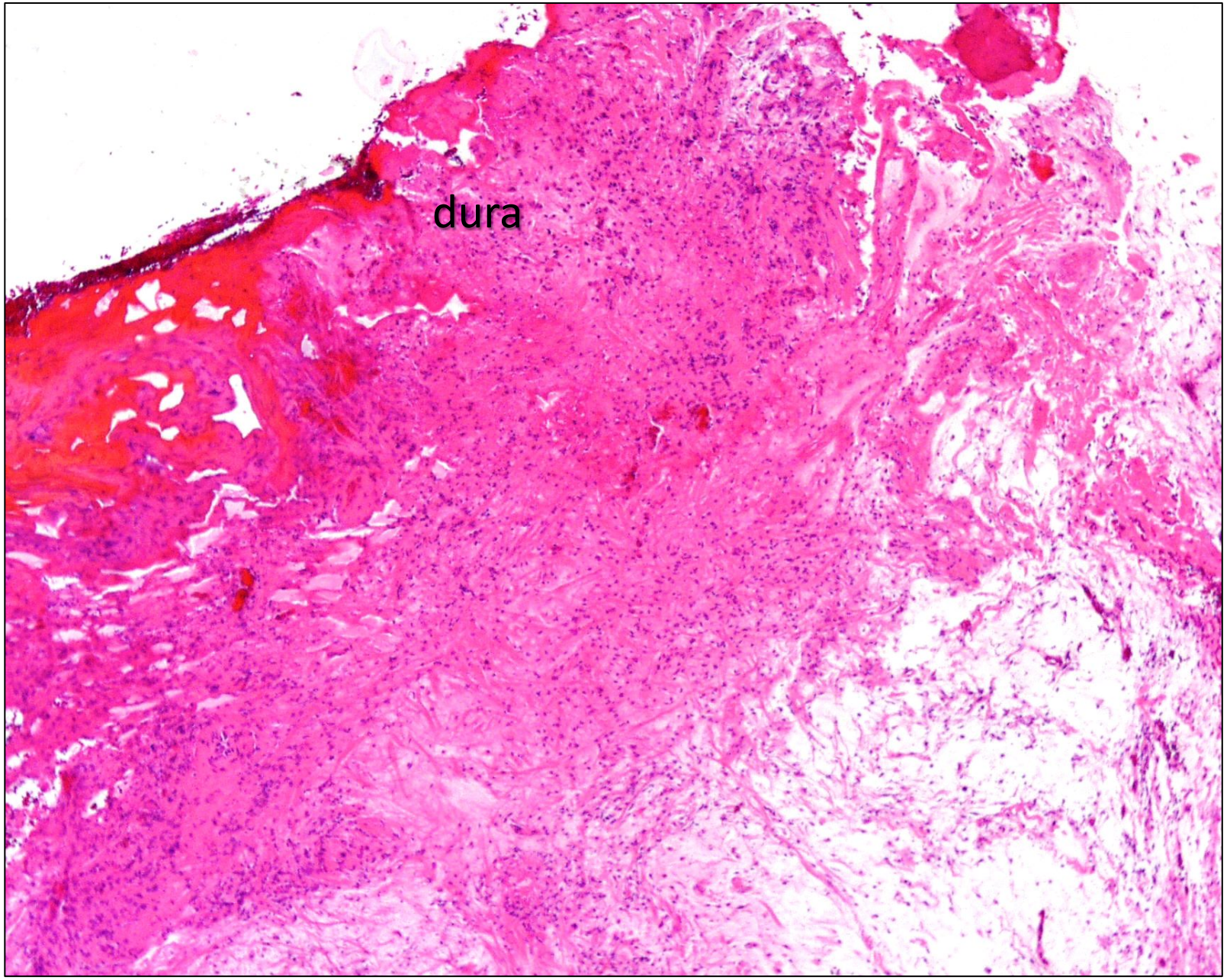


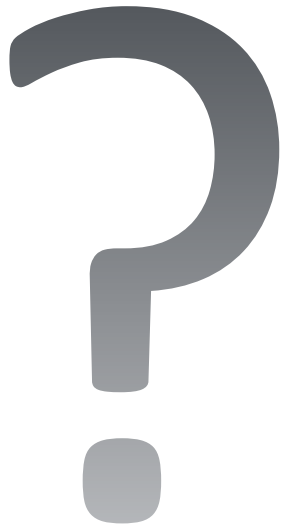
T1 Axial Post

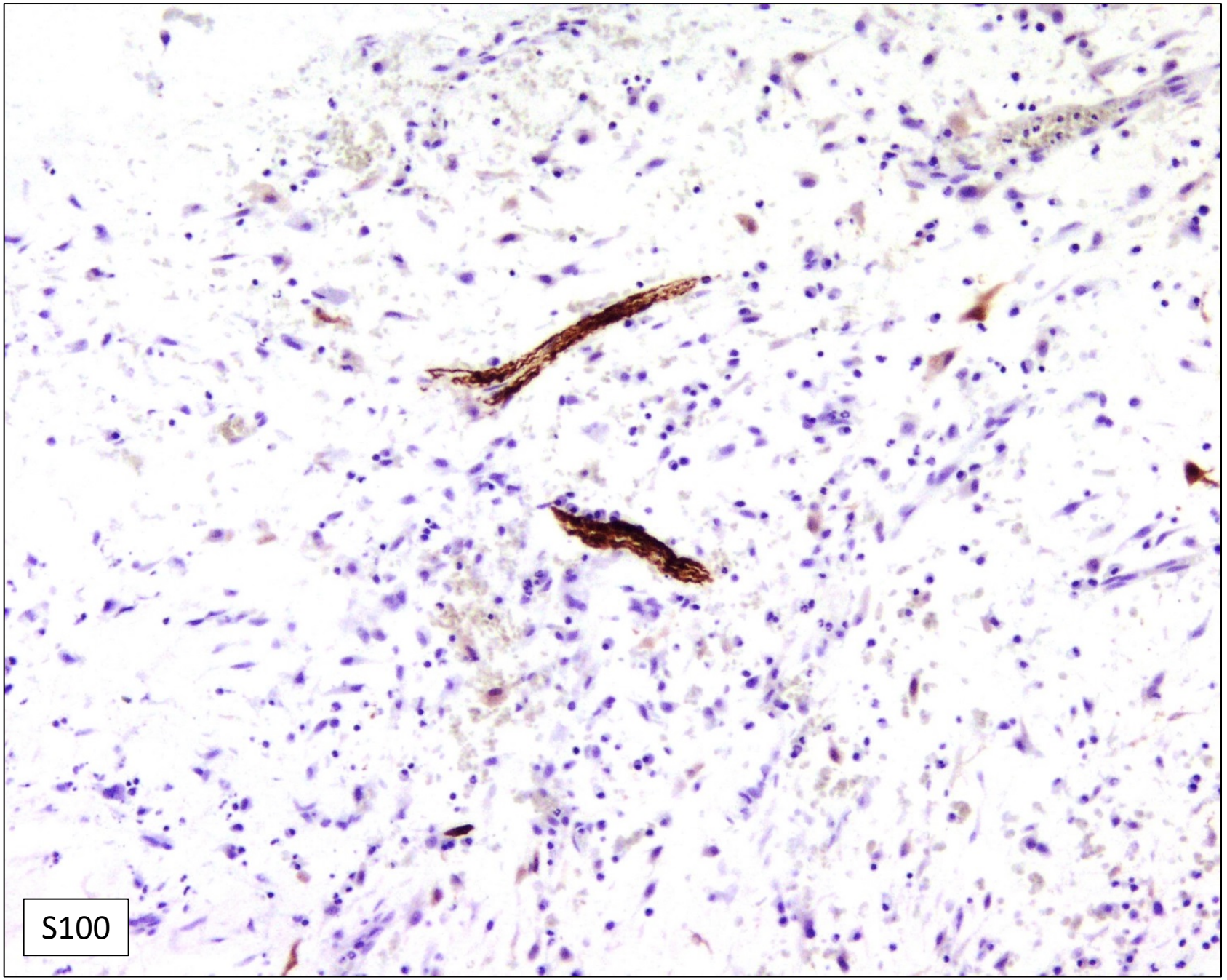
- A left retrosigmoid craniotomy and gross total resection were performed at the University of Virginia

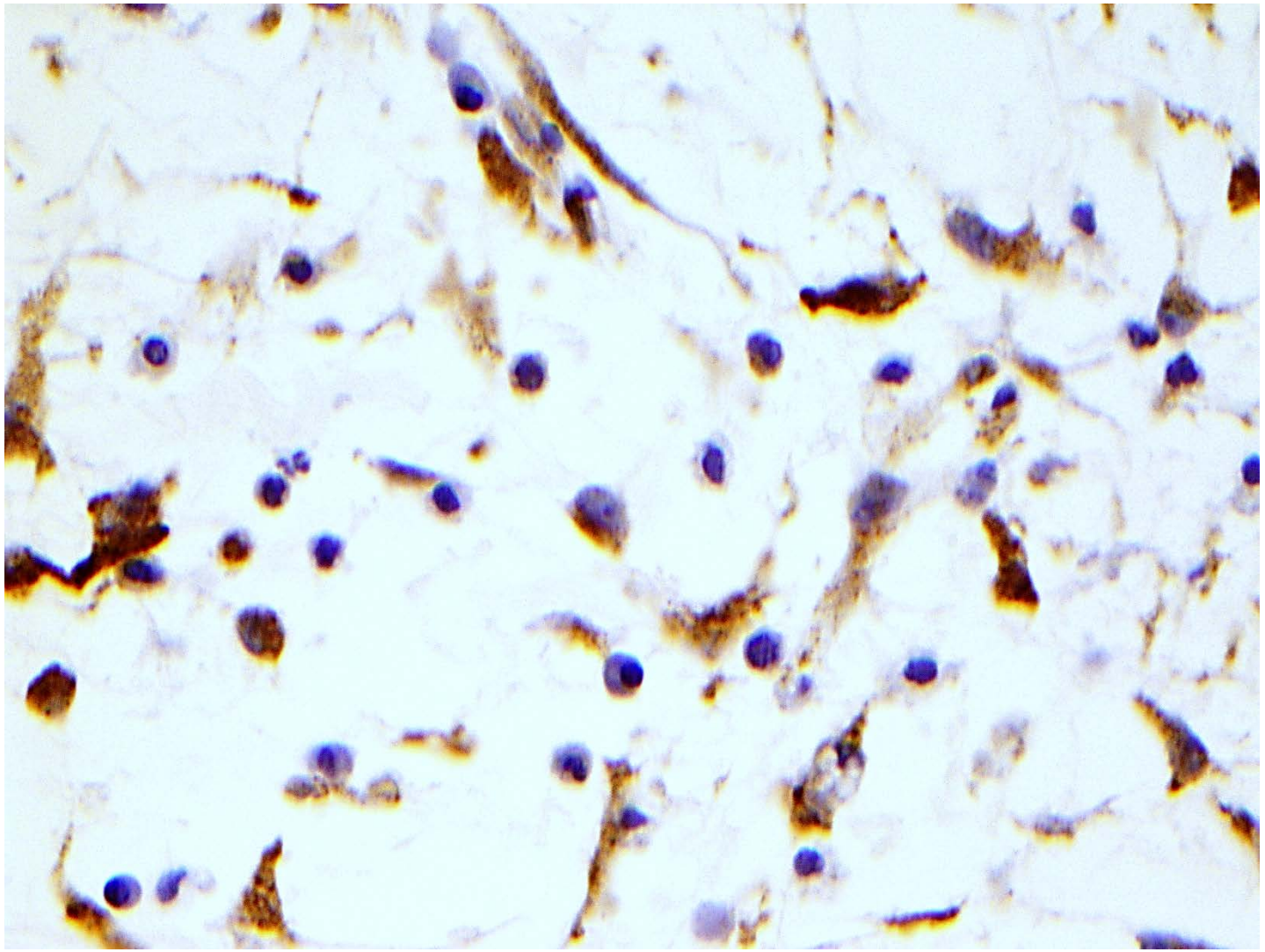




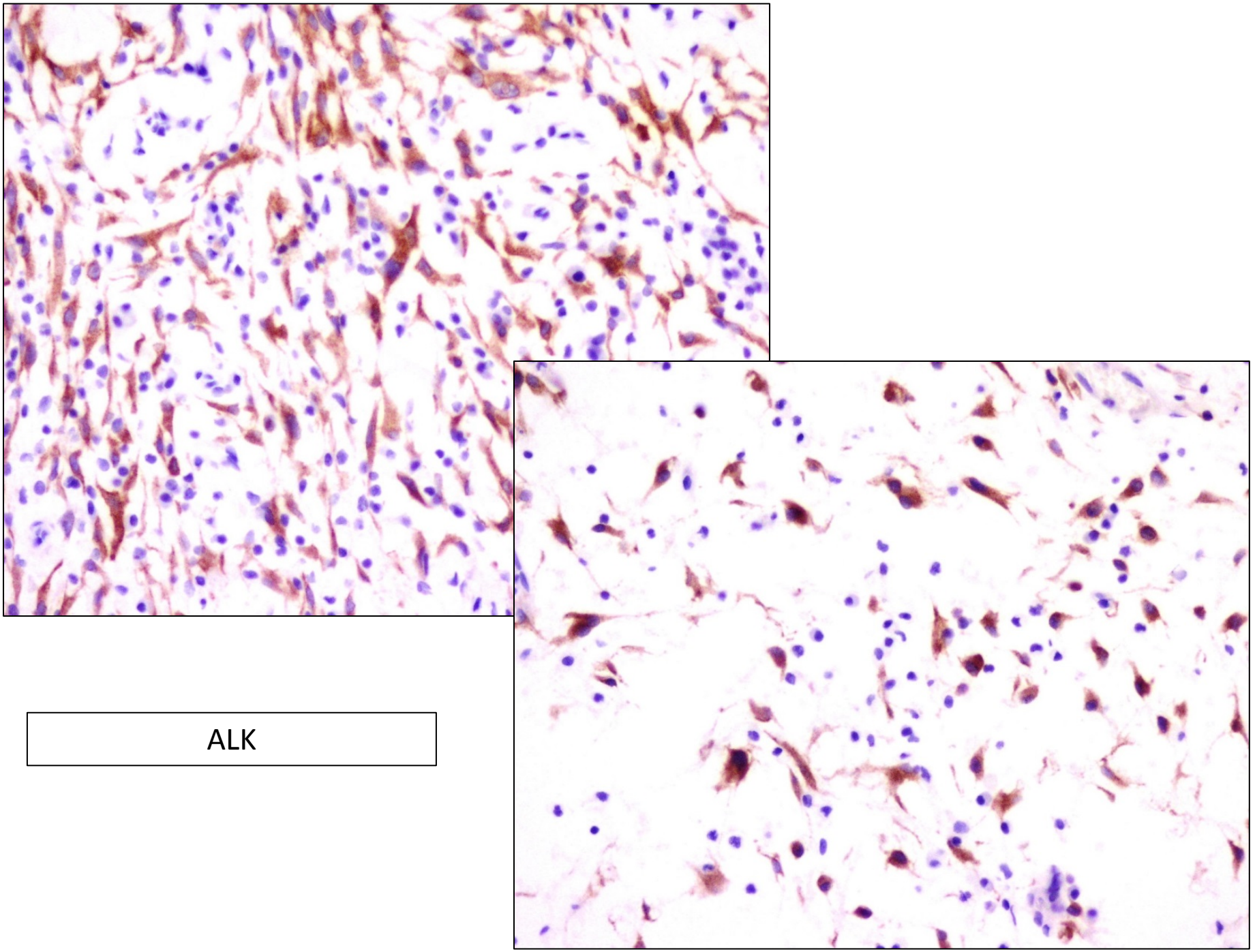

dura



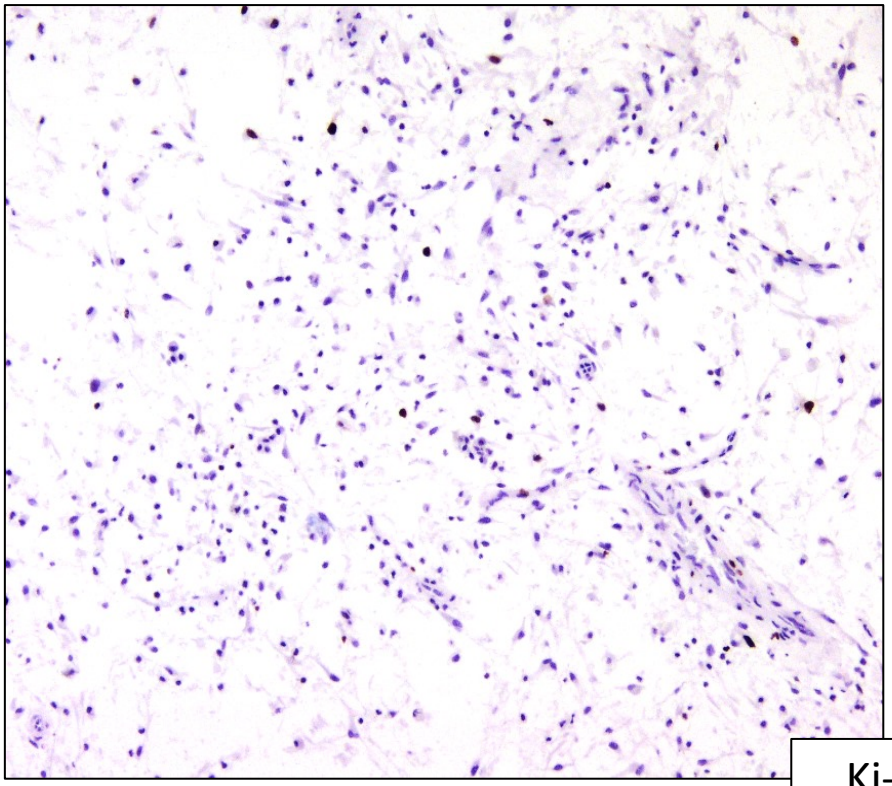

S100

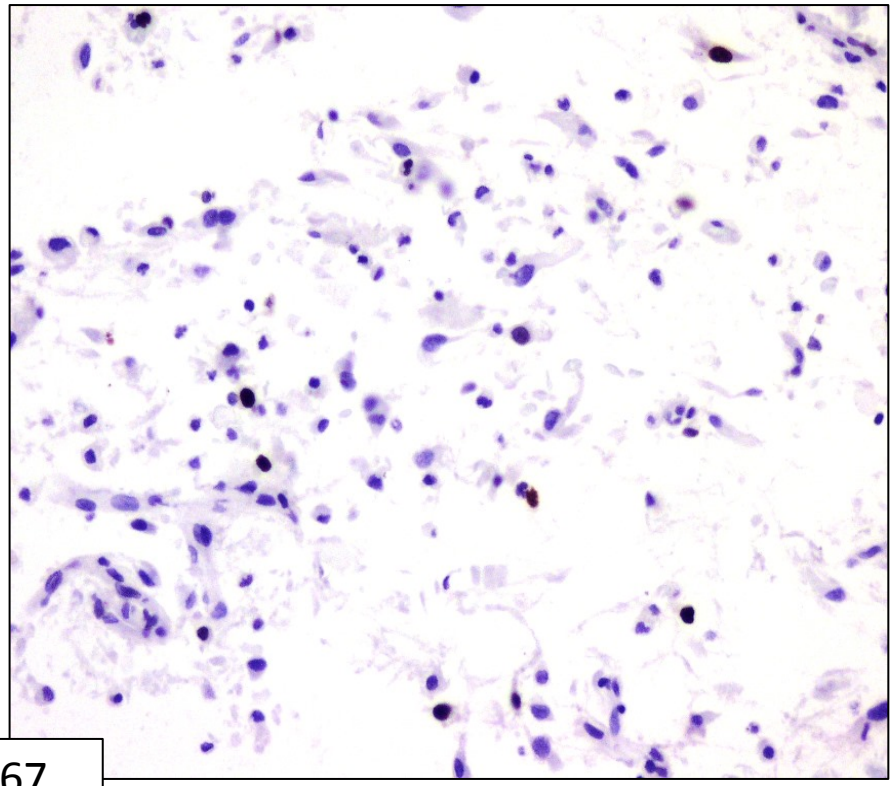


SMA



ALK





Ki-67

IHC Work-Up:

IHC Positive:

- ALK
- Focal S100
- SMA

IHC Negative:

- EMA
- Desmin
- CD34
- INI-1

Our Differential Diagnosis:

- **Inflammatory myofibroblastic tumor**
- Meningioma or chondroid tumors
- Myxoid neurofibroma
- Fibromyxoid sarcoma
- Liposarcoma
- Rhabdomyosarcoma

FISH negative:

- ALK rearrangement
- EWSR1 rearrangement

Working Diagnosis:

Proliferative spindle cell process with findings most consistent with

Inflammatory Myofibroblastic Tumor

Next step: Sent the case out to Dr. Cristina Antonescu (MSKCC) for further consultation and molecular profiling.

MSKCC – Dr. C. Antonescu Diagnosis:

- FISH analysis showed **no gene rearrangements** in ALK, ROS1, RET, PDGFRB, EWSR1, and FUS.

- **Dx:**
  - Unusual myxoid spindle cell neoplasm showing co-expression of ALK and S100.

St. Jude CRH – Dr. David Ellison:

- **Dx:**
  - Low-grade myxoid mesenchymal neoplasm with ALK expression, suggestive of inflammatory myofibroblastic tumor.

- Each consult recommended further molecular testing by NGS / RNA sequencing to determine the status of the ALK gene.

FOUNDATION MEDICINE®

- Genomic Alterations Identified:
  - ***ALK* DCTN1-ALK Fusion**

- Previously reported in IMT's in 2012. Not in CNS or pediatric patients.

- The structure of the fusion protein retains the cytoskeleton-associated protein–glycine domain and coiled coil domain of **dynactin 1** and the receptor tyrosine kinase domain of anaplastic lymphoma kinase.

- This novel fusion gene is structurally similar to other previously described anaplastic lymphoma kinase fusion genes and may be associated with the unusual morphology and immunophenotype of this tumor.

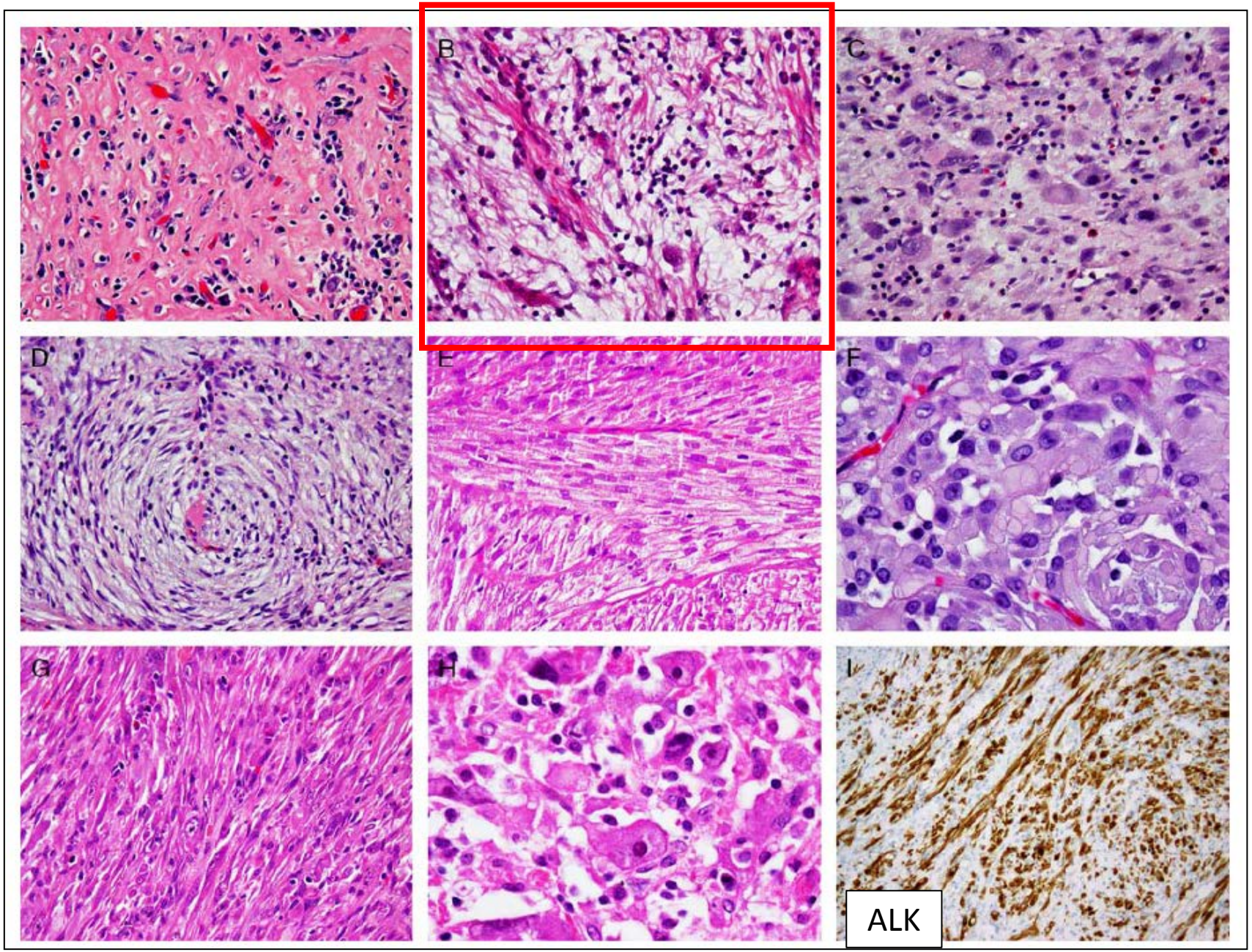
FINAL DIAGNOSIS:

INFLAMMATORY MYOFIBROBLASTIC TUMOR

***ALK* DCTN1-ALK Fusion**

IMT – Pathology

- Classified as a ***mesenchymal neoplasm of intermediate biological potential***
- Wide morphologic spectrum, ranging from
  - an inflammatory "pseudotumor" (predominant hyalinization and chronic inflammation and only a paucity of lesional spindle cells)
  - to a highly cellular myofibroblastic proliferation and
  - occasionally frankly sarcomatous neoplasm, lacking significant inflammatory or/and fibromyxoid stromal component
- About 50% of the IMTs harbor a clonal translocation that activates the *ALK* (anaplastic lymphoma kinase) gene located at the 2p23 locus
  - Several ALK fusion partners, rearrangements / translocations
  - Other less common gene rearrangements: *ROS1*, *PDGFR, RET (*Antonescu C et al. AJSP 2015; PMID: 25723109)
- In total, about 70% of children IMTs have some gene rearrangement
- As a result, ALK protein is overexpressed and can be detected by IHC level, being used as a reliable diagnostic marker for this disease



Antonescu CR et al. *Am J Surg Pathol*. 2015 Jul; 39(7): 957-967

IMT-CNS and Treatment: Surgery with an overall recurrence rate 18.5%

- Brain and Spine locations.
- Recurrence may be local and/or multicentric
- May early or late, by as much as 10+ years

At Last Follow-Up Visit: ~5 Months

- Treatment: Gross total resection.
- The patient is healthy-appearing and well-nourished. His weight is at the 82nd percentile, consistent with his growth curve.
- He has no focal neurologic deficits.
- G-Tube was removed.
- No new notes in the last three months.
- Follow-Up in 1 year.

The End.

Questions?

Thank You!!

References:

Antonescu CR, Suurmeijer AJ, Zhang L, et al. Molecular characterization of inflammatory myofibroblastic tumors with frequent ALK and ROS1 fusions and rare novel *RET* gene rearrangement. *Am J Surg Pathol*. 2015;39(7):957-967. PMID: 25723109

Chougule A, Bal A, Das A, et al. A comparative study of inflammatory myofibroblastic tumors and tumefactive IgG4-related inflammatory lesions: the relevance of IgG4 plasma cells. *Appl Immunohistochem Mol Morphol*. 2016 Nov/Dec;24(10):721-728. PMID: 26469330

Denis DJ, Elayoubi K, Weil AG, Berthelet F, Bojanowski MW. Inflammatory myofibroblastic tumors of the central nervous system that express anaplastic lymphoma kinase have a high recurrence rate. *Surgical Neurology International*. 2013;4:70. PMID: 23776756

Jeon YK, Chang KH, Suh YL, Jung HW, Park SH. Inflammatory myofibroblastic tumor of the central nervous system: clinicopathologic analysis of 10 cases. *J Neuropathol Exp Neurol*. 2005 Mar;64(3):254-9. PubMed PMID: 15804057

Telugu RB, Prabhu AJ, Kalappurayil NB, et al. Clinicopathological study of 18 cases of inflammatory myofibroblastic tumors with reference to ALK-1 expression: 5-year experience in a tertiary care center. *J Pathol Transl Med*. 2017 May;51(3):255-263. PMID: 28415158

Wang X, Krishnan C, Nguyen EP, Meyer KJ, Oliveira JL, Yang P, Yi ES, Erickson-Johnson MR, Yaszemski MJ, Maran A, Oliveira AM. Fusion of dynactin 1 to anaplastic lymphoma kinase in inflammatory myofibroblastic tumor. Hum Pathol. 2012 Nov;43(11):2047-52. PMID: 22658521

Zemmoura I, Hamlat A, Morandi X. Intradural extramedullary spinal inflammatory myofibroblastic tumor: case report and literature review. *European Spine Journal*. 2011;20(Suppl 2):330-335. PMID: 21465290

IMT-CNS and Treatment: Surgery with an overall recurrence rate 18.5%

TABLE 1. Clinical, Radiologic, and Histologic Features of IMTs-CNS

Patient No.	Sex/Age (years)	Chief Complaint	Location	Radiology	Therapy	Follow-up	Gross Type	Histologic Type
1	M/43	Dizziness	Orbit, falx, sup. sagittal sinus, tentorium and mastoid with brain invasion	Infiltrative enhancing meningeal thickening with venous sinus thrombosis and perilesional brain edema	STR and RT	Recurrence twice, 12 and 15 years later	P	PCG-like
2	M/41		Temporal lobe, mastoid and brain invasion	Enhancing meningeal thickening with venous and transverse sinuses thrombosis with perilesional brain edema	STR	No recurrence	P	FHC
3	M/29	Aphasia and LOC	Temporal and frontal lobes with brain invasion	Enhancing leptomeningeal thickening with perilesional brain edema	Biopsy and steroid	No recurrence	P	PCG-like
4	F/60	Back pain	Lumbar spine	Enhancing intradural extramedullary mass	GTR	No recurrence	M	PCG-like
5	M/31	Headache and ptosis	Cavernous sinus	1.5 cm-sized well-enhanced mass and cavernous sinus	GTR	No recurrence	M	FHC
6	M/42		Galea and subdura	Enhancing leptomeningeal thickening	GTR	No recurrence	P	PCG-like
7	F/65		Occipital area	4 cm-sized heterogeneously enhancing dura-based mass	GTR	Recurrence after 7 years	M	FHC
8	M/50	Seizure and headache	Frontal area	5 cm-sized extra-axial dura based enhancing mass	STR	No recurrence during 5 years	M	FHC
9	F/52	Seizure	Parietooccipital area	Enhancing nodular mass with meningeal thickening	GTR		M	PCG-like
	F/24	Diplopia	Orbit with intracranial extension	Enhanced mass with perilesional brain edema	GTR	No recurrence during 5 years	M	FHC

of consciousness; STR, subtotal resection; RT, radiotherapy; GTR, gross total resection; F[illegible]en plaque-like gross [illegible]attern; M, mass forming pattern; PCG-like, plasma cell type; FHC, fibrohistiocytic variant.

J Neuropathol Exp Neurol
Vol. 64, No. 3
March 2005
pp. 254–259

ORIGINAL ARTICLE

Inflammatory Myofibroblastic Tumor of the Central Nervous System: Clinicopathologic Analysis of 10 Cases

Yoon Kyung Jeon, MD, PhD, Kee-Hyun Chang, MD, PhD, Yeon-Lim Suh, MD, PhD, Hee Won Jung, MD, PhD, and Sung-Hye Park, MD, PhD

Eur Spine J (2011) 20 (Suppl 2):S330–S335
DOI 10.1007/s00586-011-1783-9

CASE REPORT

Intradural extramedullary spinal inflammatory myofibroblastic tumor: case report and literature review

Ilyess Zemmoura · Abderrahmane Hamlat · Xavier Morandi

Table 1 Cases of intradural extramedullary spinal inflammatory myofibroblastic tumor

	Age/sex	Location	Physical examination	Time to diagnosis (months)	MRI characteristics			Treatment	Postoperative neurological state	Recurrent (R)/ multicentric (M)	Follow-up (months)
					T1	T1 Gado	T2				
Eimoto et al. [5]	37/M	C4–C5	Spinal cord compression	12	NA	NA	NA	GTR + radiotherapy	No deficit	No	9
Mirra et al. [10]	39/F	C7	Spinal cord compression	NA	NA	NA	NA	GTR	Improvement until recurrence	R	36
Hsiang et al. [6]	57/M	T3, T12–L3, falx cerebri	Radicular pain and spinal cord compression	6	NA	+	NA	GTR	No deficit	R and M	84 (7 years)
Hsieh et al. [7]	37/M	T5, T12–L1	Back pain and spinal cord compression	6	Hypo	NA	NA	GTR	No deficit	M	14
Lacoste-Collin et al. [9]	22/F	T9 then diffuse	Back pain and spinal cord compression	3	Iso	+	Iso-hypo	Sub-total resection	Slow recovery	R and M	24
Brandsma et al. [4]	33/F	C6–C7, cranial nerves	Radicular pain and spinal cord compression	NA	NA	NA	NA	Surgery	No improvement	M	NA
Jeon et al. [8]	60/F	Lumbar spine	Back pain	NA	NA	NA	NA	GTR	NA	No	NA
Boutarbouch et al. [3]	30/F	C4–T2	Spinal cord compression	2	Iso	NA	Hypo	GTR	Progressive recovery	No	6
Yoon et al. [11]	56/F	L5	Low back pain	48	Iso	+	Iso	GTR + interbody fusion	No pain, toe paresthesia	No	24
Present case	43/M	C6–T1	Radicular pain	4	Iso	+	Hypo	GTR	Incomplete recovery	No	14

M male, *F* female, *Gado* gadolinium, *NA* not available, + enhancement after gadolinium infusion, *hypo* hypointense, *iso* isointense, *GTR* gross total resection