Hereditary Tumor Syndromes

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AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose

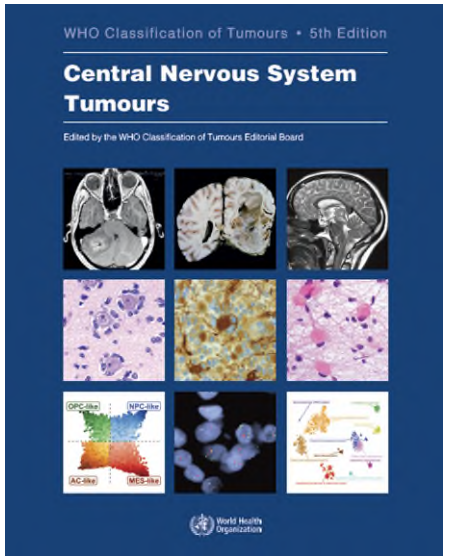
Learning Objectives

At the end of this activity learners should be able to:

- Identify at least three hereditary tumor syndromes that commonly present with tumors of the nervous system.
- Recognize at least three CNS or PNS tumor types that are highly associated with specific hereditary tumor syndromes.
- Discuss the role of the neuropathologist in establishing a hereditary tumor syndrome diagnosis and the implications for both the patient and their family.

14.0: Genetic tumour syndromes involving the CNS (and PNS)

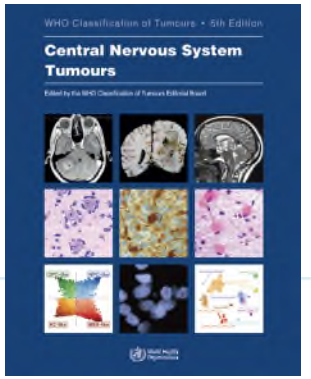
14.0.0.1: Genetic tumour syndromes of the nervous system: Introduction
14.0.0.2: Neurofibromatosis type 1
14.0.0.3: Neurofibromatosis type 2
14.0.0.4: Schwannomatosis
14.0.0.5: Von Hippel-Lindau syndrome
14.0.0.6: Tuberous sclerosis
14.0.0.7: Li-Fraumeni syndrome
14.0.0.8: Cowden syndrome
14.0.0.9: Constitutional mismatch repair deficiency syndrome
14.0.0.10: Familial adenomatous polyposis 1
14.0.0.11: Naevoid basal cell carcinoma syndrome
14.0.0.12: Rhabdoid tumour predisposition syndrome
14.0.0.13: Carney complex
14.0.0.14: DICER1 syndrome
14.0.0.15: Familial paraganglioma syndromes
14.0.0.16: Melanoma-astrocytoma syndrome
14.0.0.17: Familial retinoblastoma
14.0.0.18: BAP1 tumour predisposition syndrome
14.0.0.19: Fanconi anaemia
14.0.0.20: ELP1-medulloblastoma syndrome



Hereditary Tumor Syndrome Concepts

- Wide range of phenotypes and penetrance
- Implications for entire family; genetic counseling
- Evolving clinical and genetic diagnostic criteria
- Highly complex and require multidisciplinary care
- **Neuropathologists not infrequently get the first clues or are the first ones to put all the clues together**
- A syndrome may also be first suspected from results of tumor only NGS, mainly based on allelic frequencies

Tumor types that should prompt consideration of an underlying genetic tumour syndrome

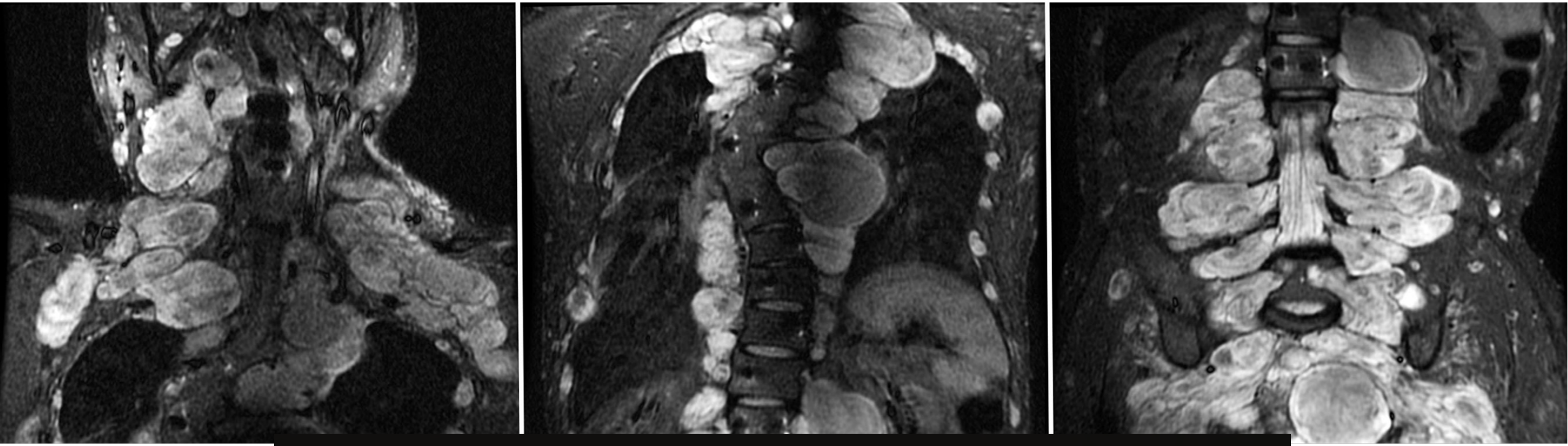


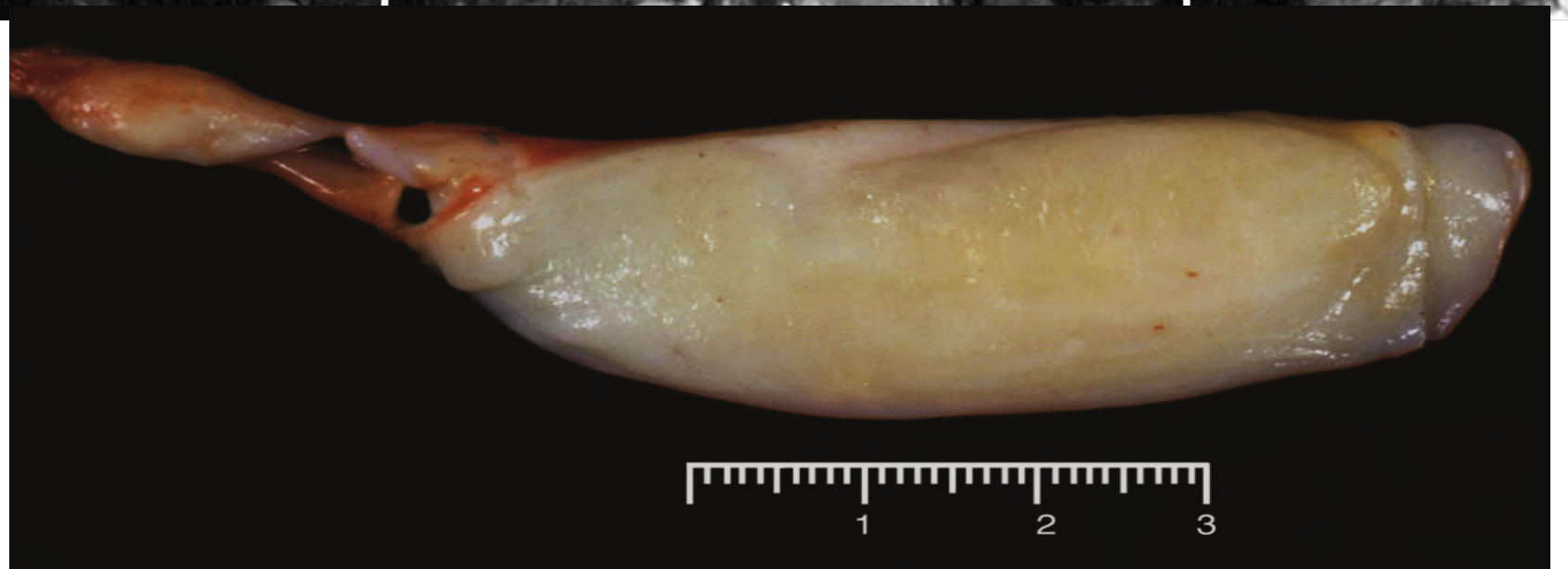
Source:

Tumour scenario	Genetic tumour syndrome(s)
Bilateral vestibular schwannomas	NF2
Choroid plexus carcinoma	Li–Fraumeni syndrome
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	Cowden syndrome
Embryonal tumour with multilayered rosettes lacking C19MC alteration	*DICER1* syndrome
Haemangioblastoma	Von Hippel–Lindau syndrome
Hybrid neurofibroma/schwannoma	NF1, NF2, and schwannomatosis
IDH- and H3-wildtype, p53-positive glioblastoma in a child	Li–Fraumeni syndrome
IDH-wildtype giant cell glioblastoma in a young patient	Constitutional mismatch repair deficiency, Lynch syndrome, and Li–Fraumeni syndrome
IDH1 p.R132C/S–mutant astrocytoma in an adult	Li–Fraumeni syndrome
Malignant melanotic nerve sheath tumour	Carney complex
Malignant peripheral nerve sheath tumour arising from a neurofibroma	NF1
Meningioma in a child	NF2
Multiple meningiomas	NF2
Multiple neurofibromas, a plexiform neurofibroma, or a massive soft tissue neurofibroma	NF1
Multiple schwannomas or one with mosaic SMARCB1 (INI1) expression	NF2 and schwannomatosis
Paraganglioma with loss of SDHB expression	Familial paraganglioma syndromes (see <<#19884>>Table 14.06, p. XXX)
Pineoblastoma	*DICER1* syndrome and familial retinoblastoma syndrome
Pituitary blastoma	*DICER1* syndrome
Primary intracranial sarcoma, *DICER1*-mutant	*DICER1* syndrome
Rhabdoid and/or papillary meningioma	*BAP1* tumour predisposition syndrome
Rhabdoid tumour(s) in an infant	Rhabdoid tumour predisposition syndrome
SHH-activated medulloblastoma	Naevoid basal cell carcinoma (Gorlin) syndrome, ELP1-medulloblastoma syndrome, and *GPR161* (Gorlin-like) syndrome
SHH-activated, *TP53*-mutant medulloblastoma (often the large cell / anaplastic histological type)	Li–Fraumeni syndrome and Fanconi anaemia
Subependymal giant cell astrocytoma	Tuberous sclerosis
WNT-activated medulloblastoma, *CTNNB1*-wildtype	Familial adenomatous polyposis

NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; SHH, sonic hedgehog.

Neurofibromas and MPNSTs in NF1





Human Pathology (2017) 67, 1–10

ELSEVIER

Current topic

New Term: ANNUBP - Atypical Neurofibromatous Neoplasm of Uncertain Biologic Potential

Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1—a consensus overview☆,☆☆

Markku M. Miettinen MD[a,*], Cristina R. Antonescu MD[b], Christopher D.M. Fletcher MD[c], Aerang Kim MD[d], Alexander J. Lazar MD[e], Martha M. Quezado MD[a], Karlyne M. Reilly PhD[f], Anat Stemmer-Rachamimov MD[g], Douglas R. Stewart MD[h], David Viskochil MD[i], Brigitte Widemann MD[j], Arie Perry MD[k]

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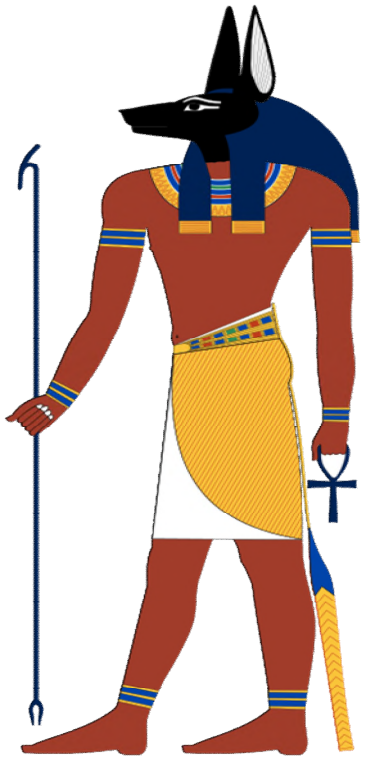
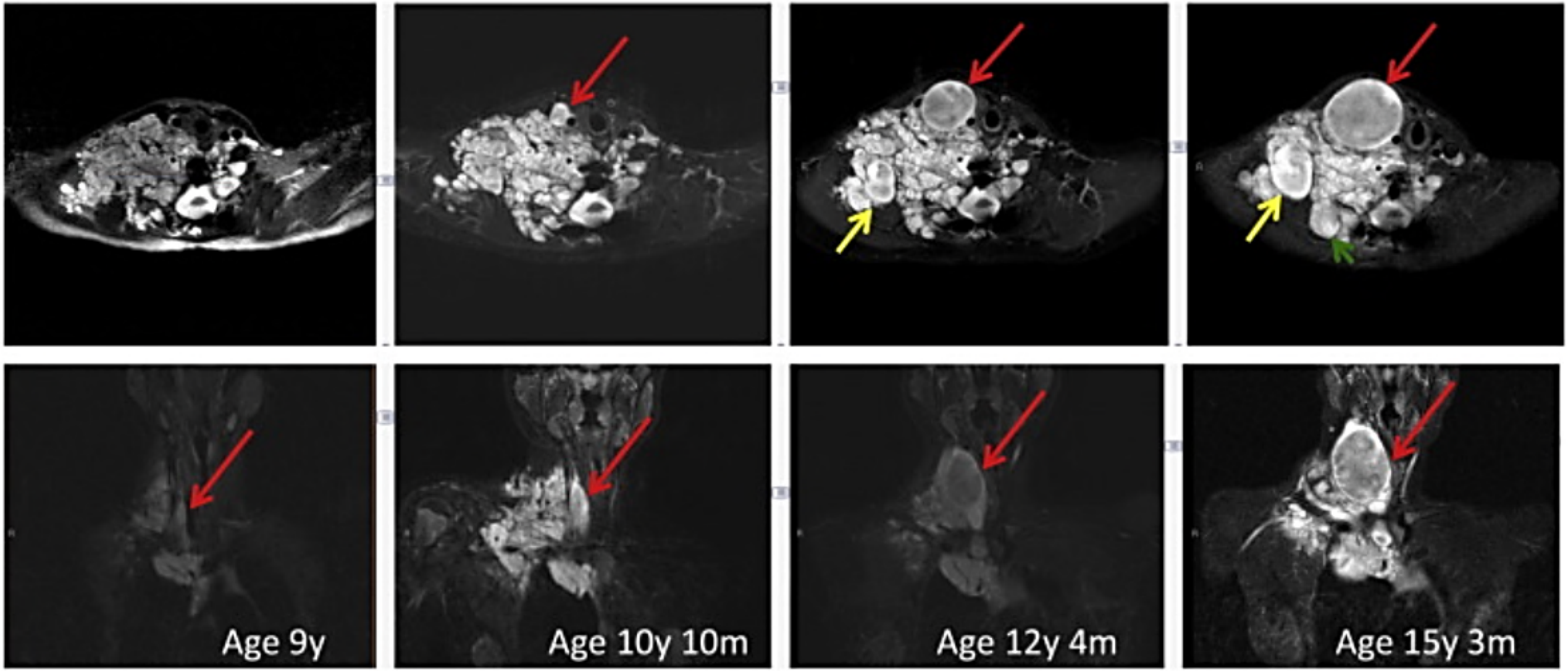


Anubis - Egyptian God of Afterlife

ANNUBP and LG-MPNST more frequent due to surveillance



Miettinen M et al., Hum Pathol 67:1-10, 2017

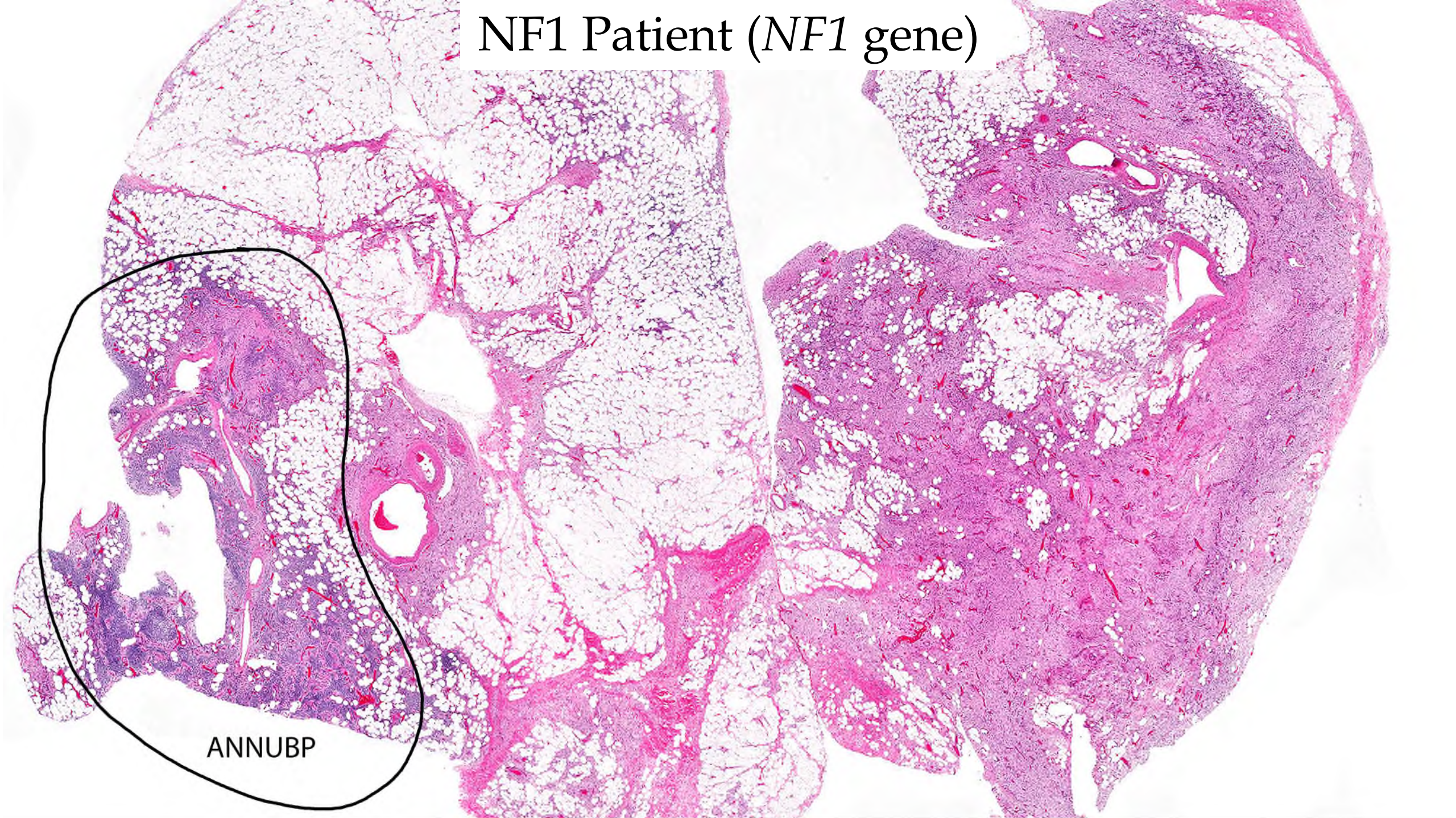
Diagnosis	Proposed definition
Neurofibroma (NF)	Benign Schwann cell neoplasm with thin, often wavy nuclei, wispy cell processes, and a myxoid to collagenous ("shredded carrots") matrix. Immunohistochemistry includes extensive but not diffuse S100 and SOX10 positivity and a lattice-like CD34+ fibroblastic network.
Plexiform NF	NF diffusely enlarging and replacing a nerve, often involving multiple nerve fascicles, delineated by EMA+ perineurial cells
Neurofibroma with atypia ("ancient neurofibroma")	NF with atypia alone, most commonly manifesting as scattered bizarre nuclei
Cellular NF	NF with hypercellularity, but retained NF architecture and <1 mf/50 HPFs

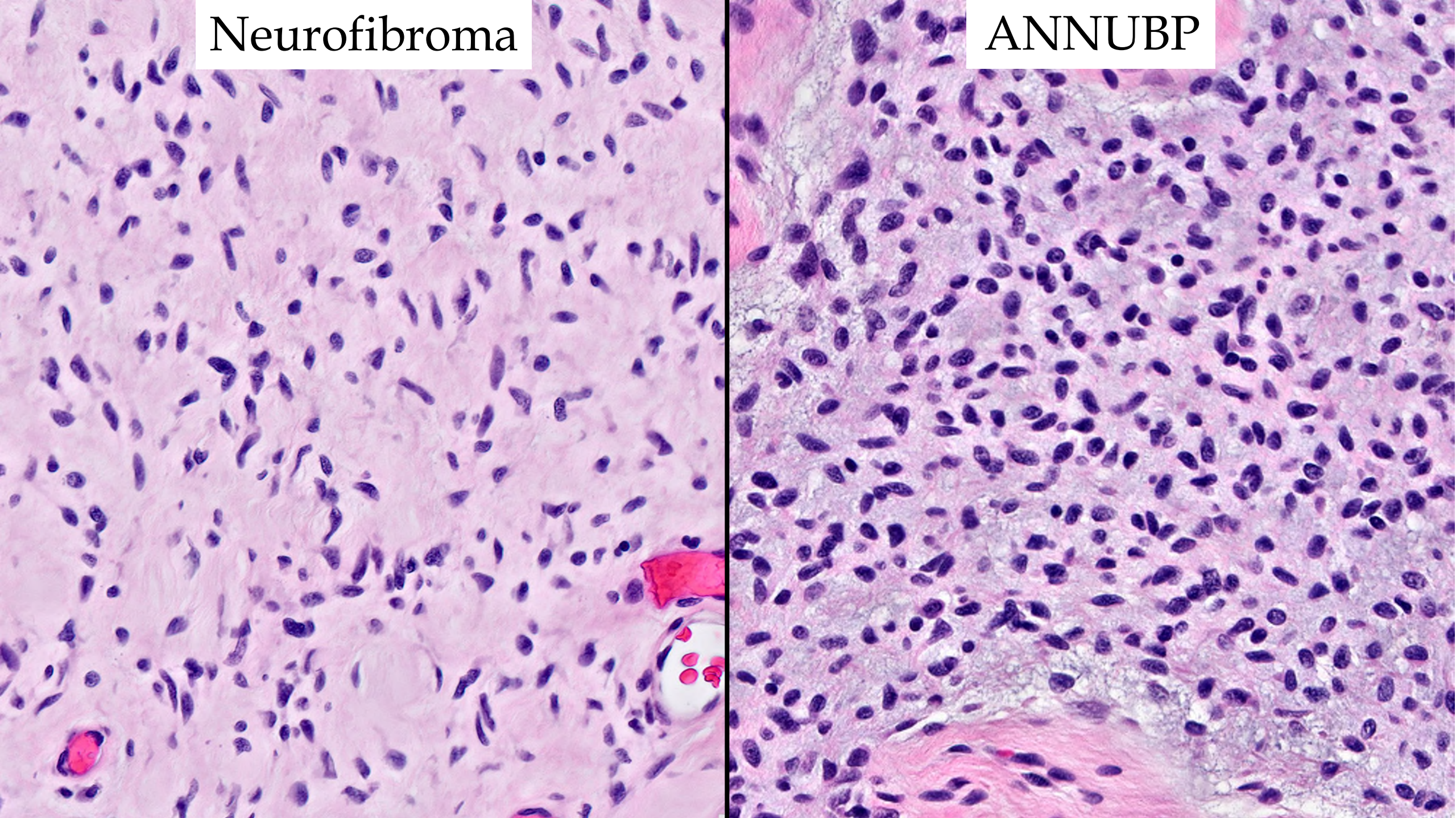
ANNUBP	Schwann cell neoplasm with at least 2 of 4 features: cytologic atypia, loss of neurofibroma architecture, hypercellularity, mitotic index >1/50 HPFs and <3/10 HPFs
MPNST, low-grade	Features of ANNUBP, but with mitotic index of 3-9/10 HPFs and no necrosis
MPNST, high-grade	MPNST with at least 10 mf/10 HPFs or 3–9 mf/10 HPFs combined with necrosis

NOTE. Loss of NF architecture refers to fascicular growth pattern and/or lack of CD34+ fibroblastic network; hypercellularity refers to "blue" appearance at low magnification and nuclear overlap at high magnification.

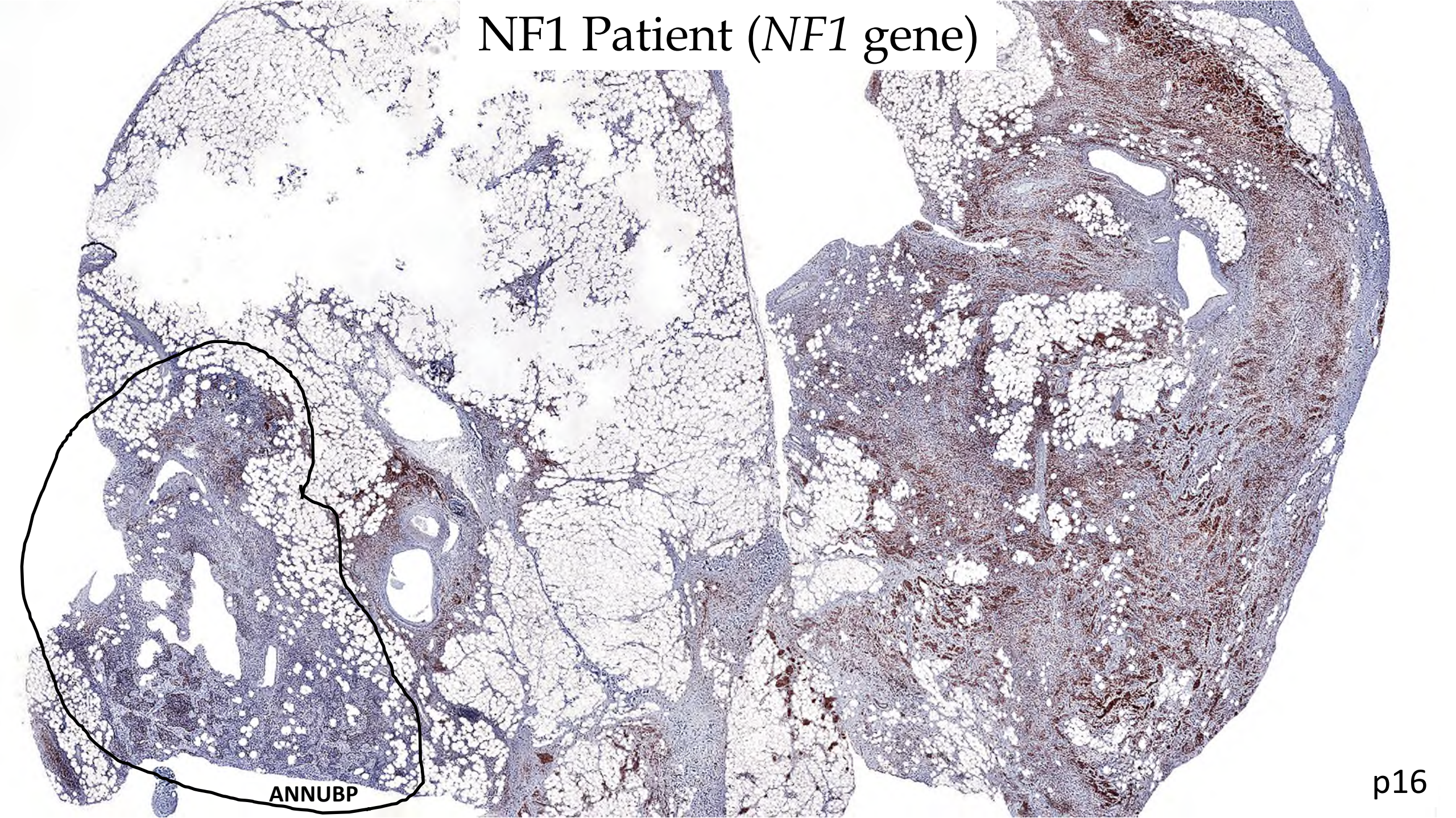
Miettinen M et al., Hum Pathol 67:1-10, 2017

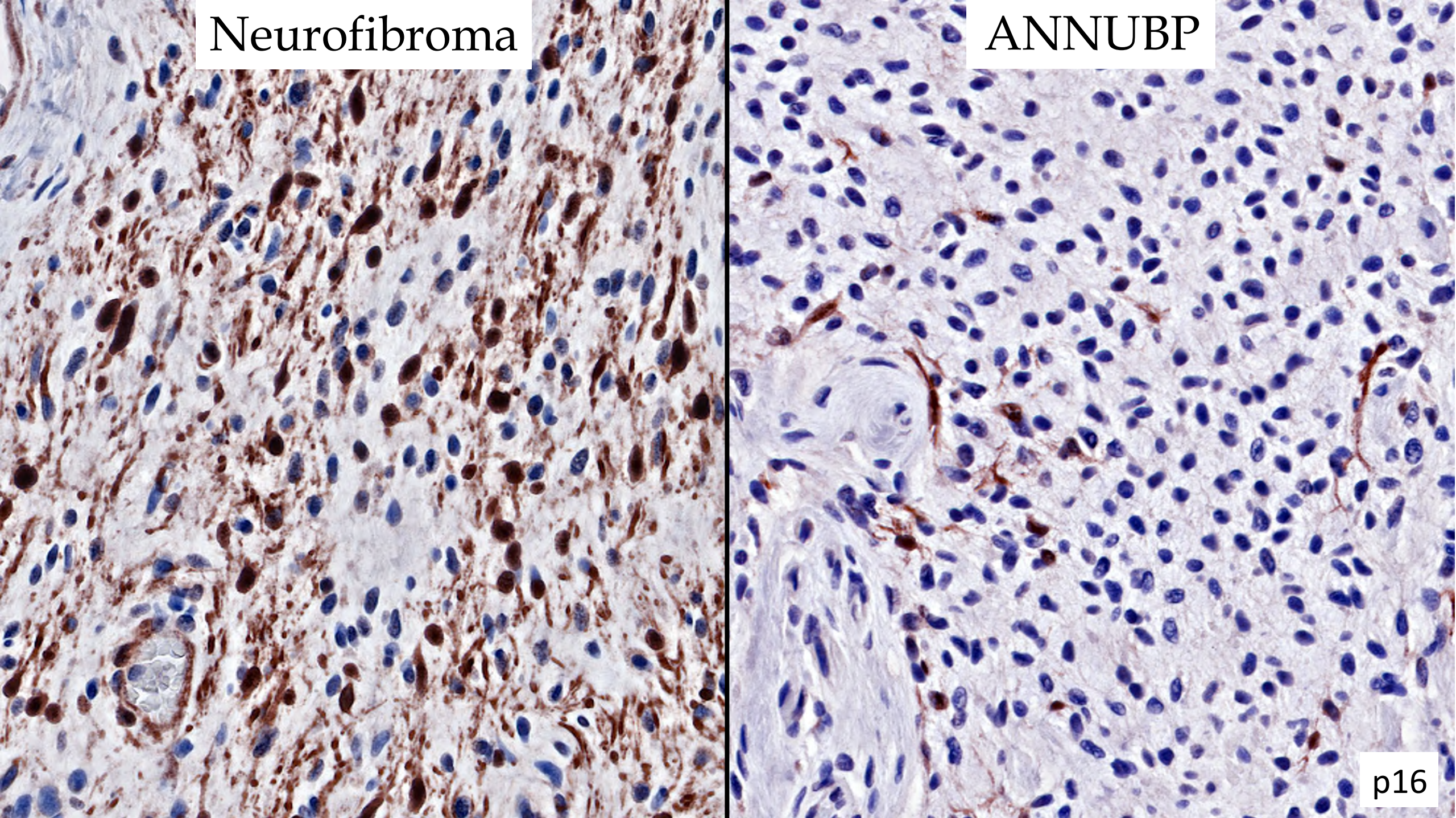
NF1 Patient (*NF1* gene)



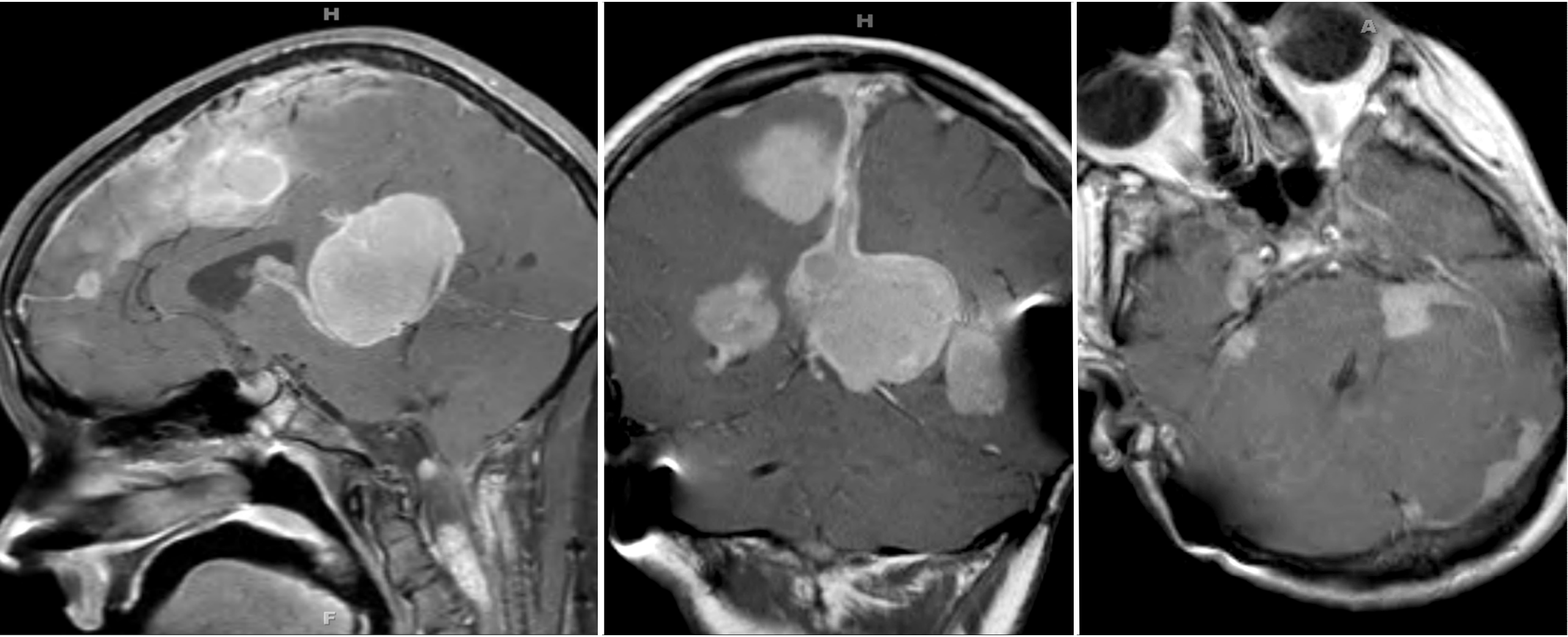

Neurofibroma
ANNUBP

NF1 Patient (*NF1* gene)

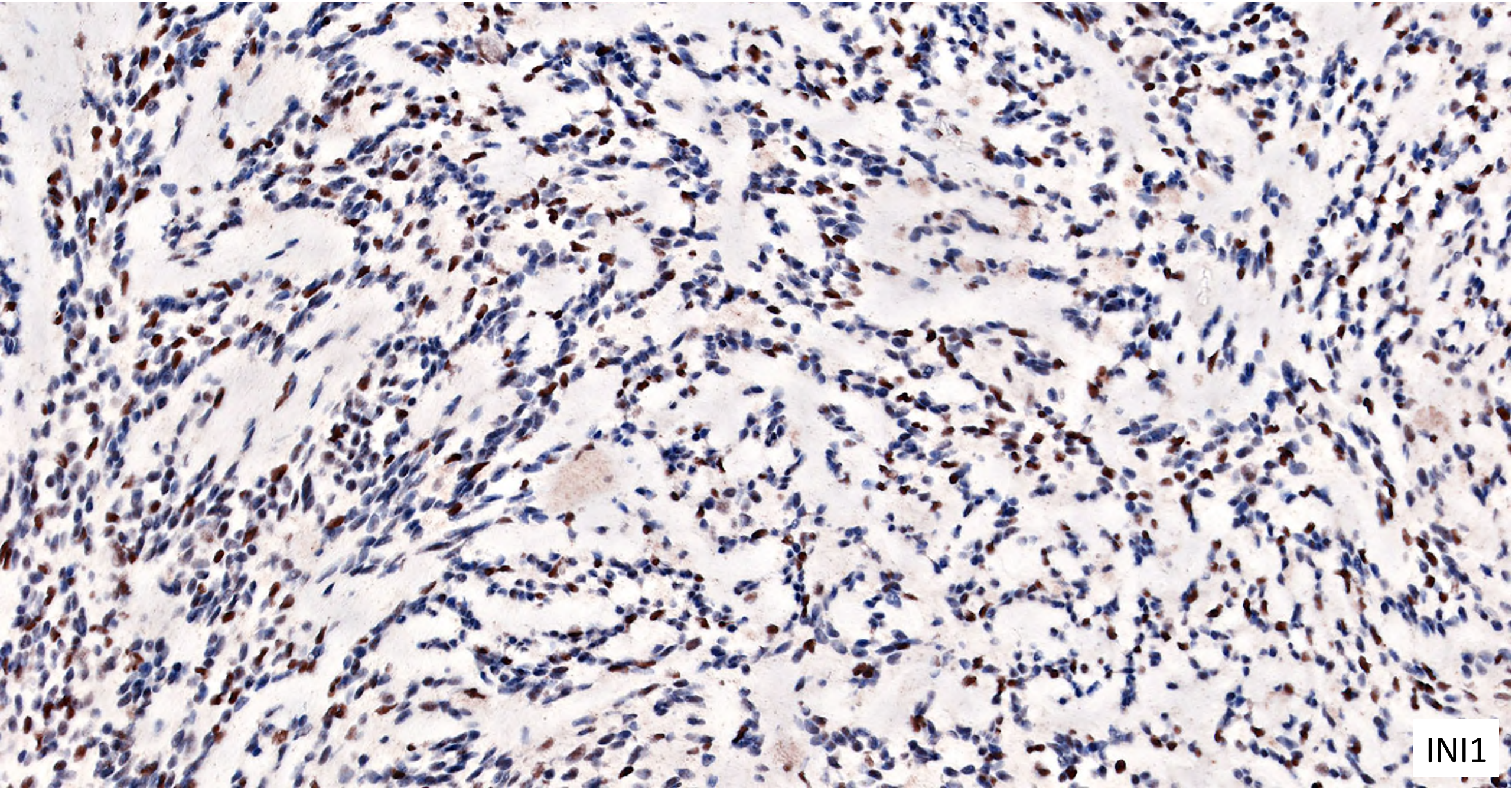



Neurofibroma
ANNUBP
p16

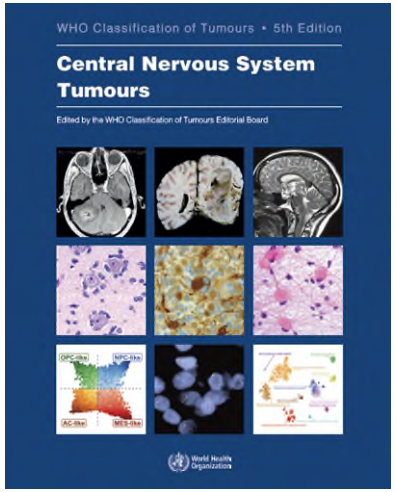
NF2 PATIENT (*NF2* gene)



Schwannoma in NF2 or Schwannomatosis (*SMARCB1, LZTR1,* or *DGCR8*)



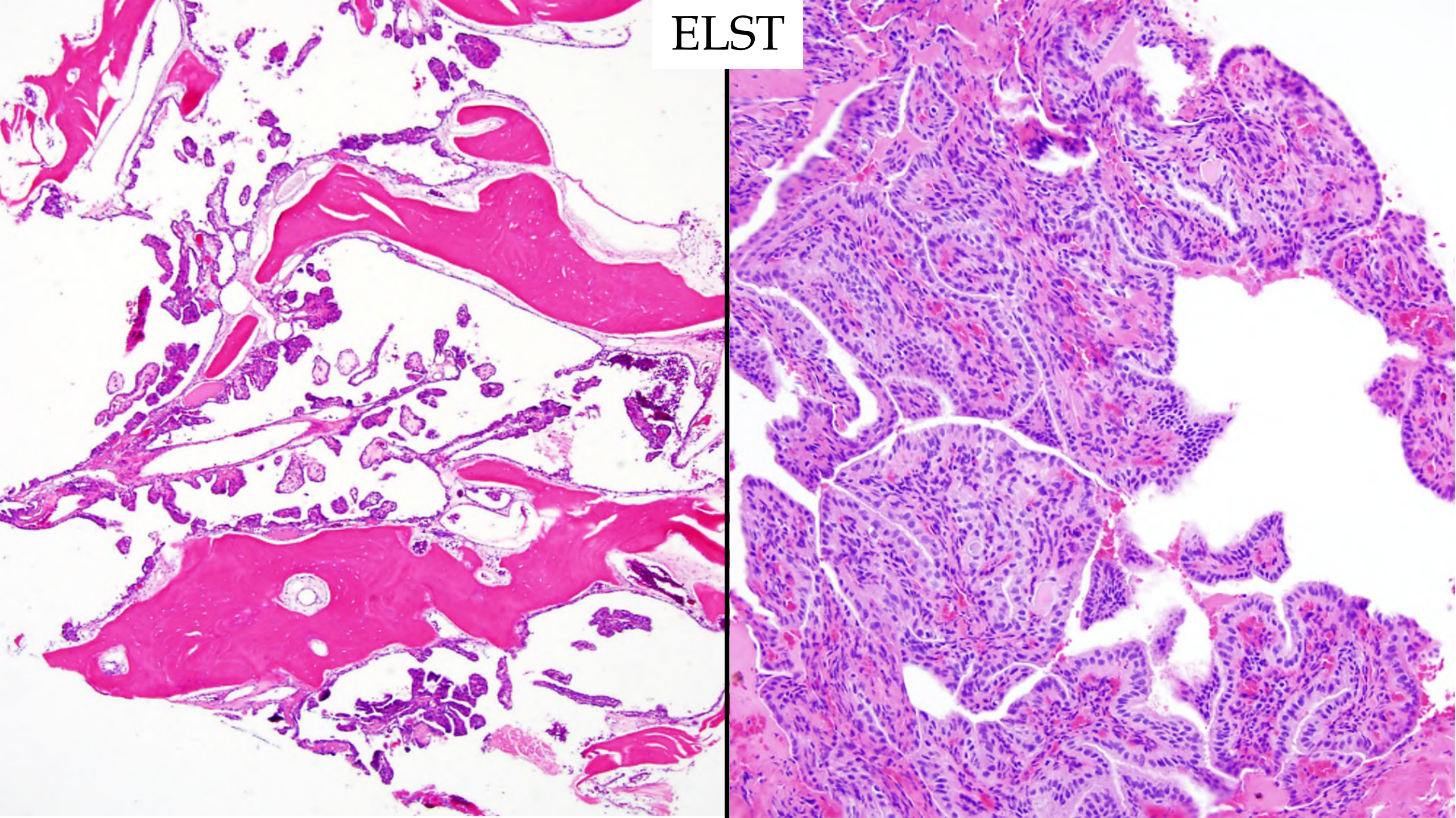
Organ/tissue distribution and pathology of lesions in von Hippel–Lindau syndrome (*VHL* gene)

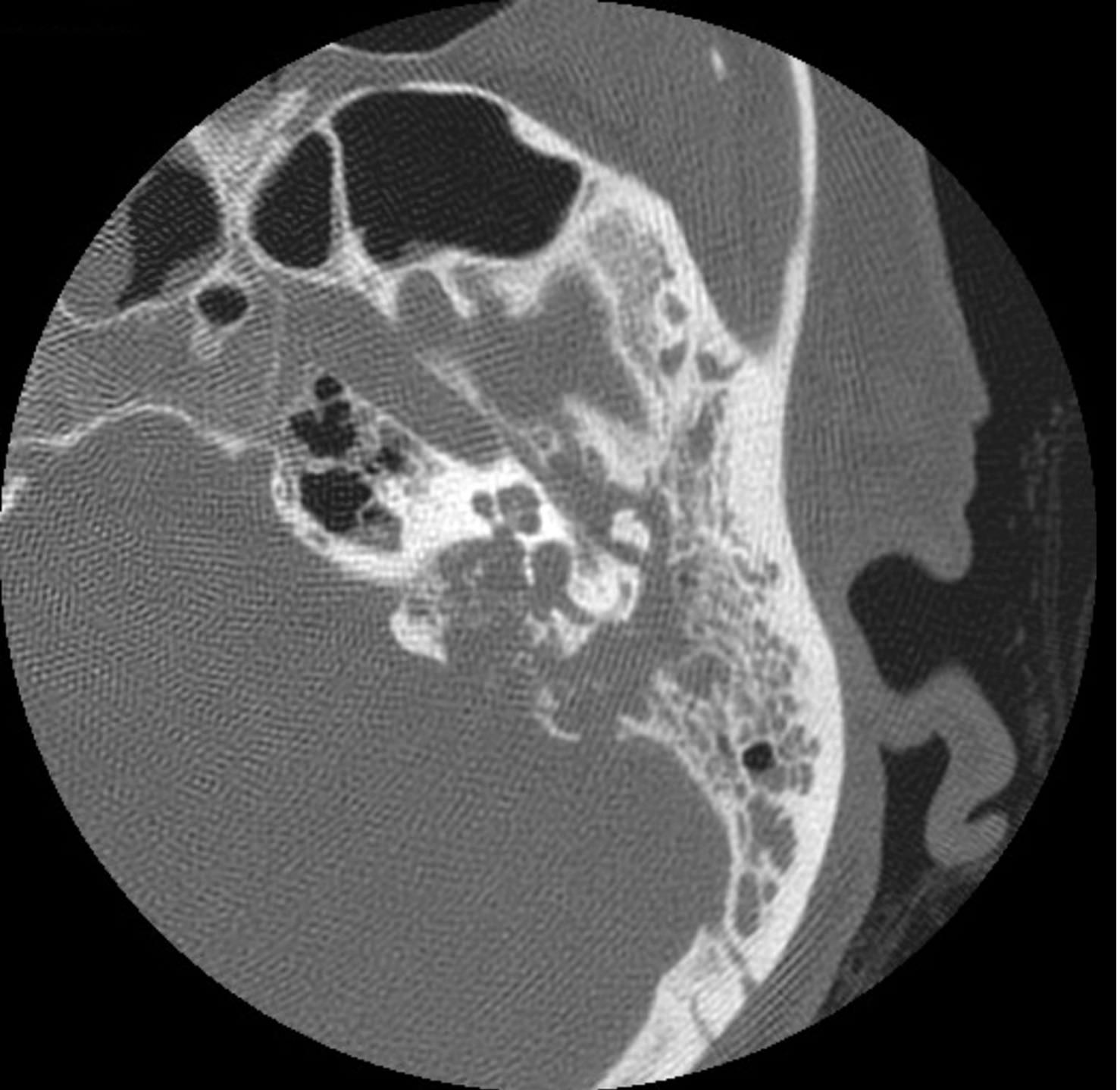


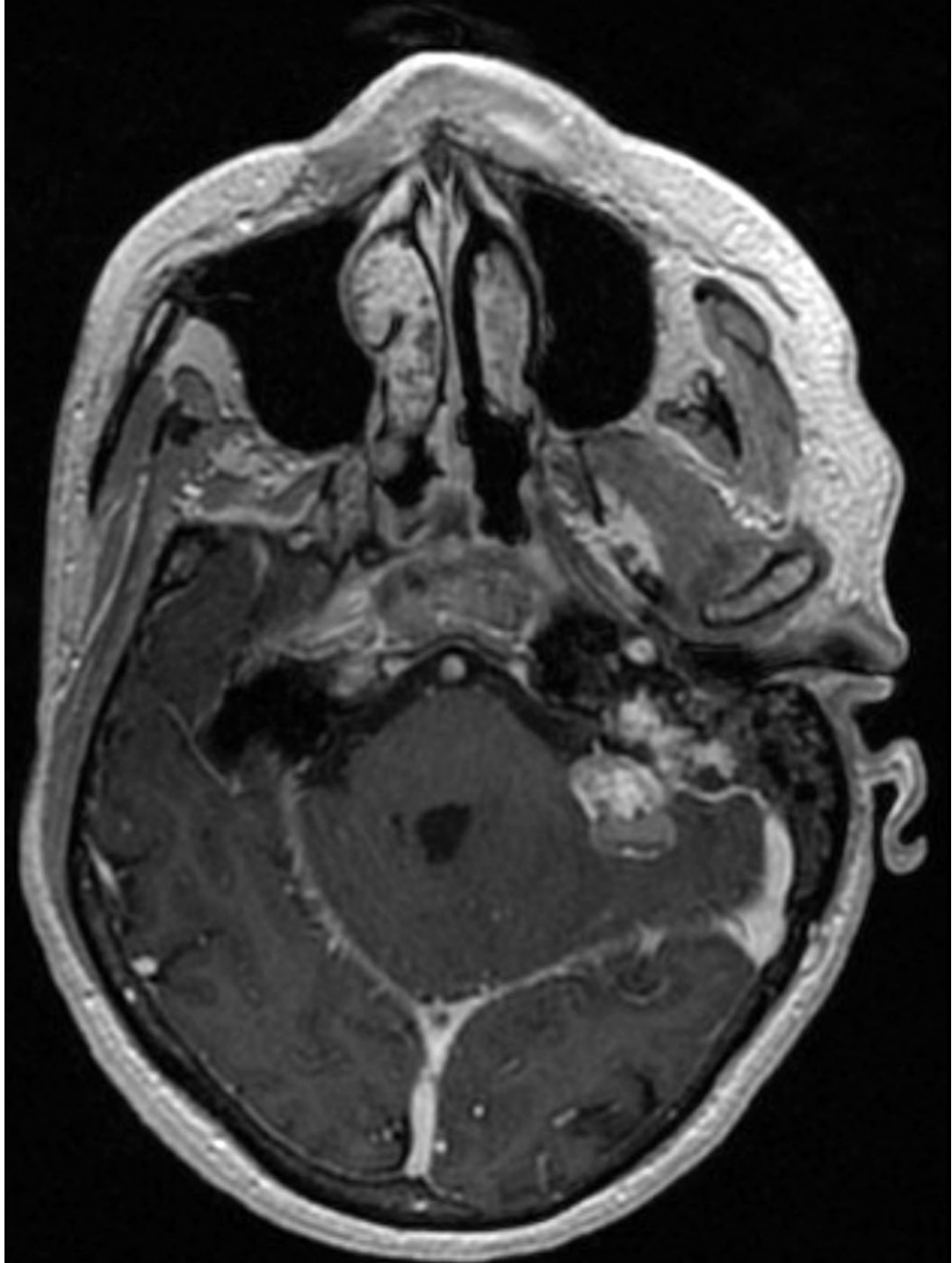
Source : Published in the previous 2016 edition of VHL disease

Organ/tissue	Tumour(s)	Non-neoplastic lesions
CNS	Haemangioblastoma	
Eye (retina)	Haemangioblastoma	
Kidney	Clear cell renal cell carcinoma	Cysts
Adrenal gland	Phaeochromocytoma	
Pancreas	Neuroendocrine islet cell tumours	Cysts
Inner ear	Endolymphatic sac tumour	
Epididymis	Papillary cystadenoma	

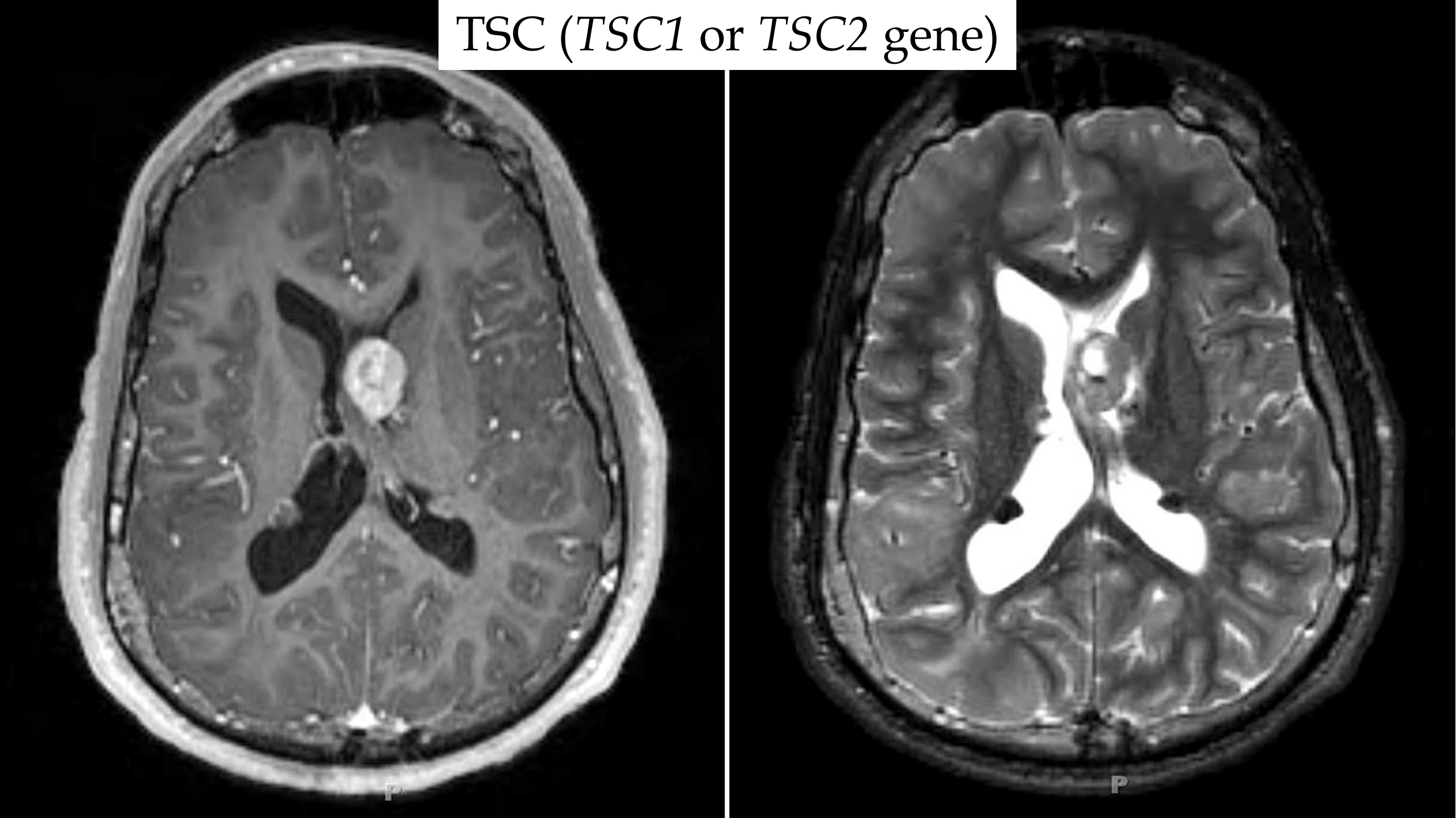
~40% of seemingly sporadic ELST assoc. with VHL


ELST

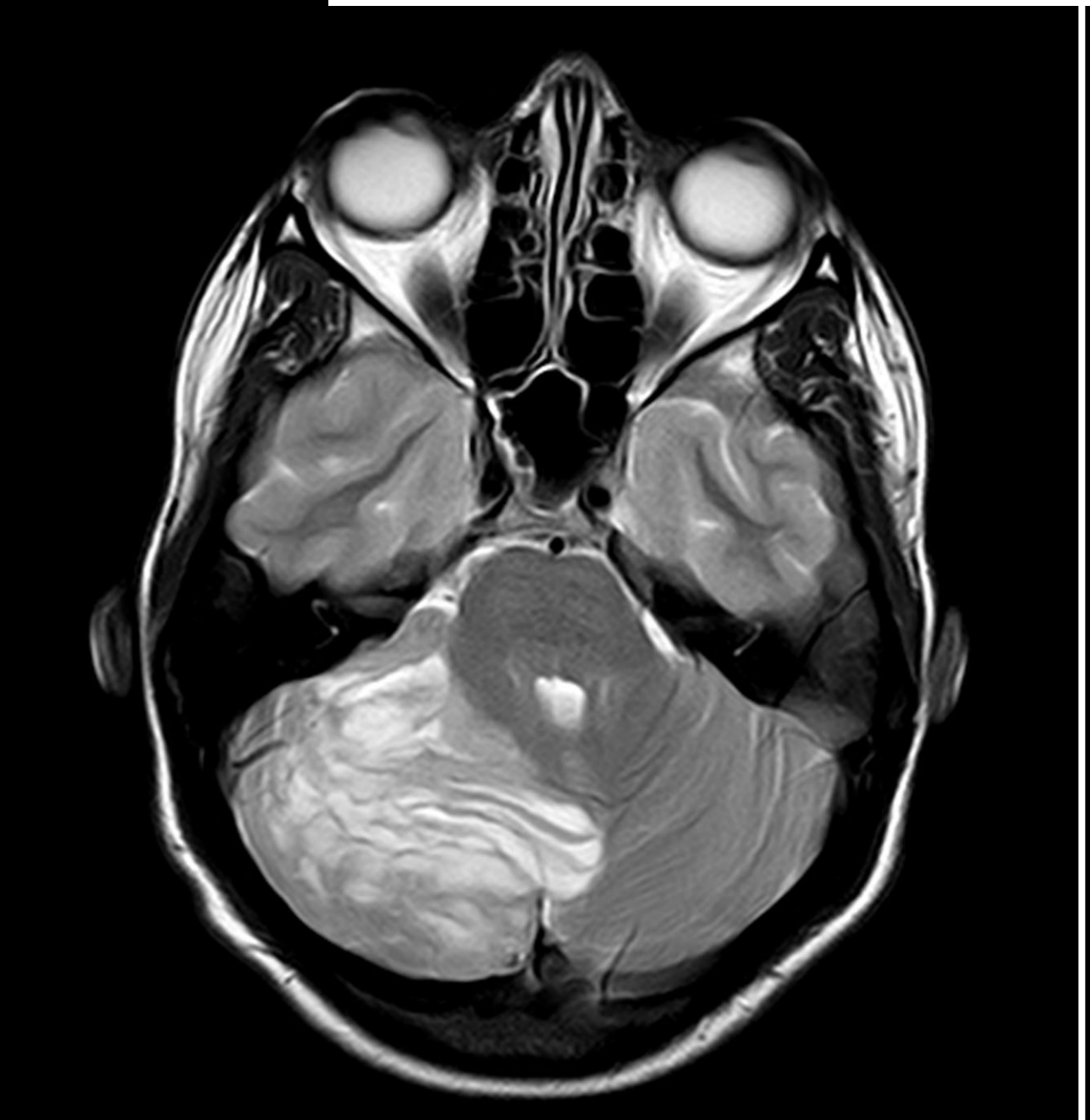


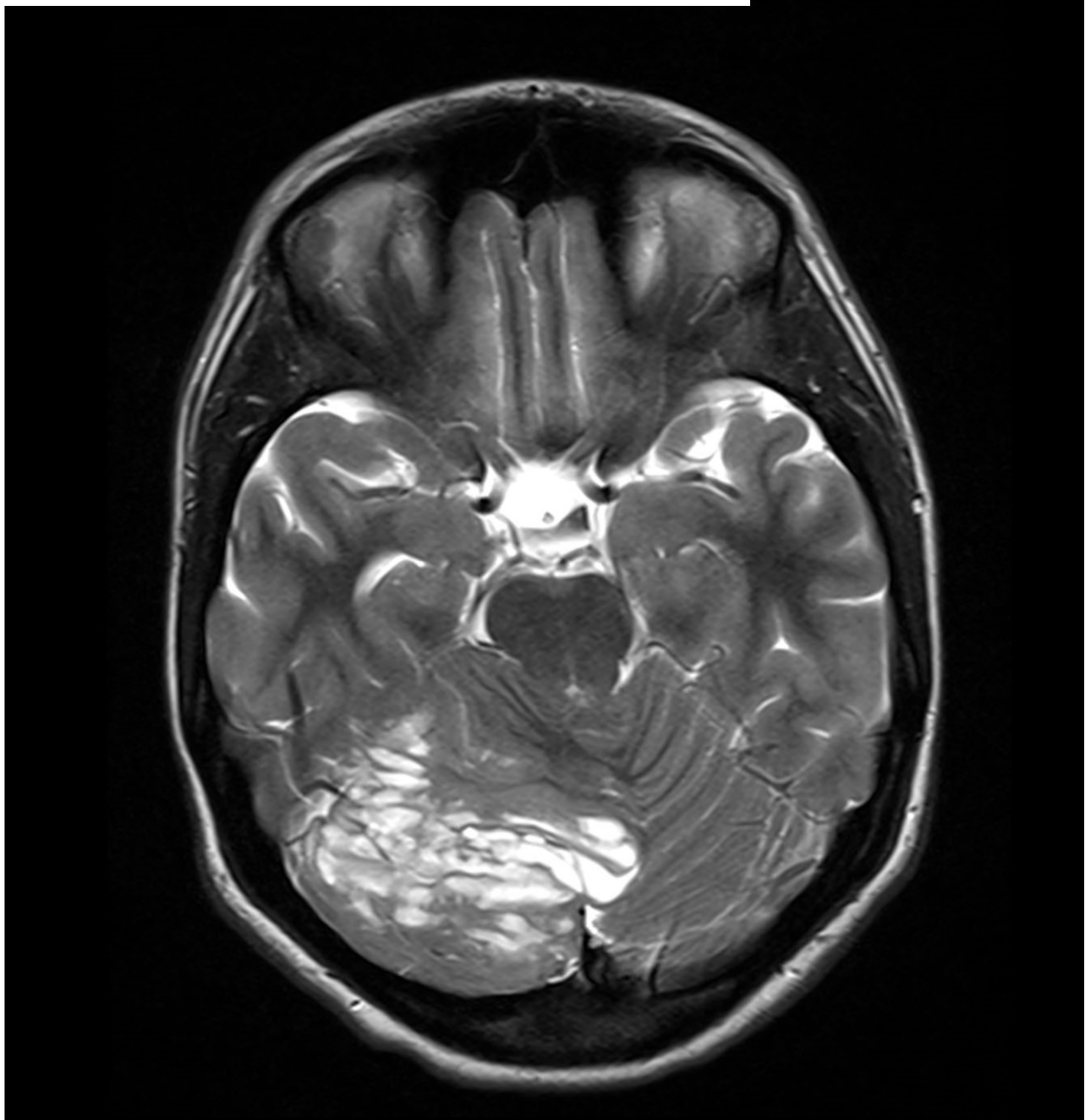


TSC (*TSC1* or *TSC2* gene)

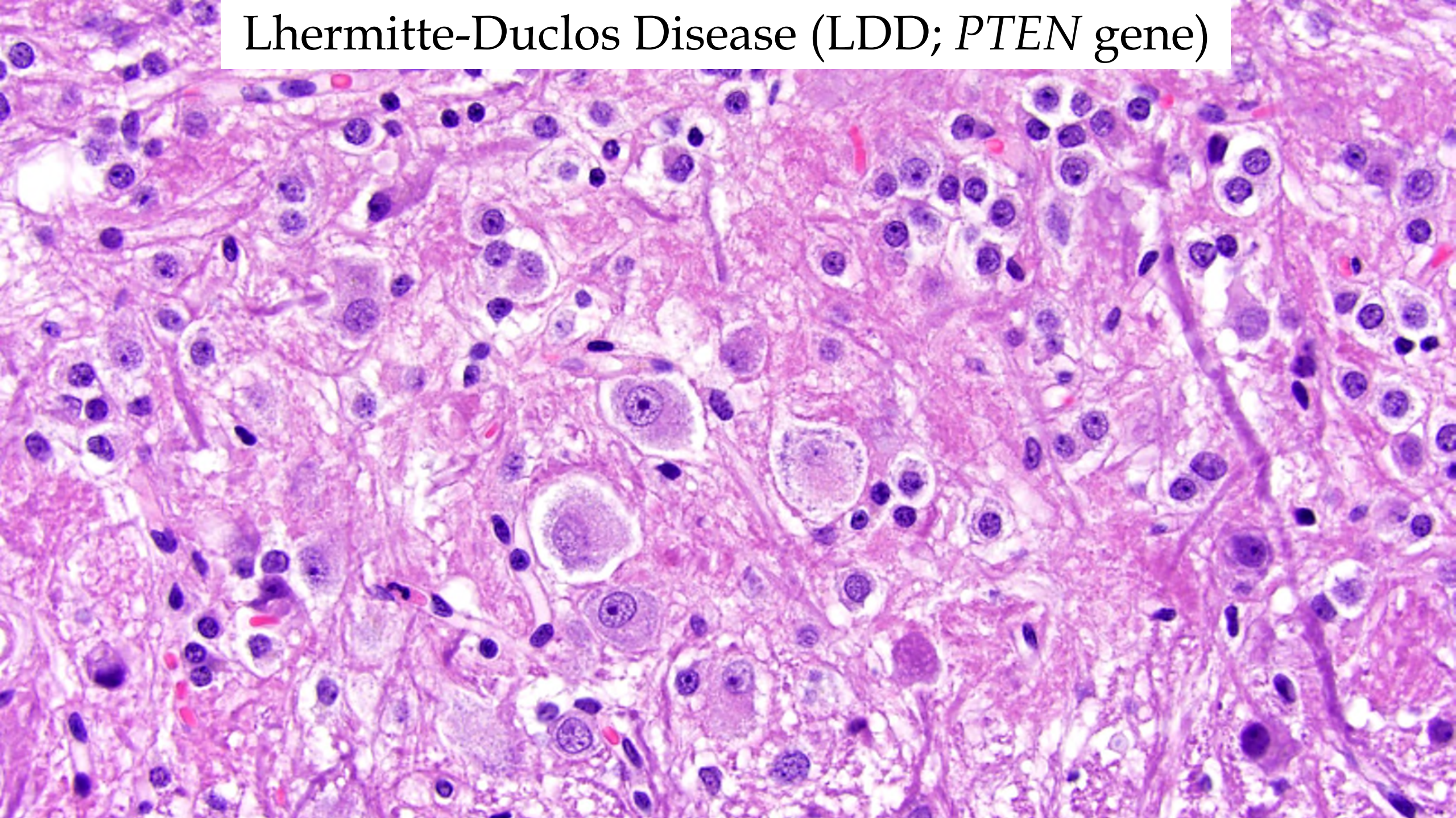


Lhermitte-Duclos Disease (LDD; *PTEN* gene)

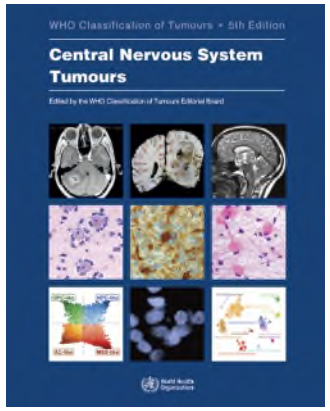




Lhermitte-Duclos Disease (LDD; *PTEN* gene)



ICC and NCCN criteria for Cowden syndrome without known family history of *PTEN* mutation



Pathognomonic criteria:

Adult dysplastic cerebellar gangliocytoma (cerebellar tumours)

Mucocutaneous lesions[a]

- Facial trichilemmomas, any number[a] (at least two biopsy-proven trichilemmomas[b])
- Acral keratoses
- Papillomatous papules

Mucosal lesions (especially hamartomatous gastrointestinal polyps)

Autism spectrum disorder and macrocephaly[b]

Major criteria:

Breast cancer

Thyroid cancer (non-medullary)

Macrocephaly (megalocephaly; i.e. 97th percentile and above)

Endometrial cancer

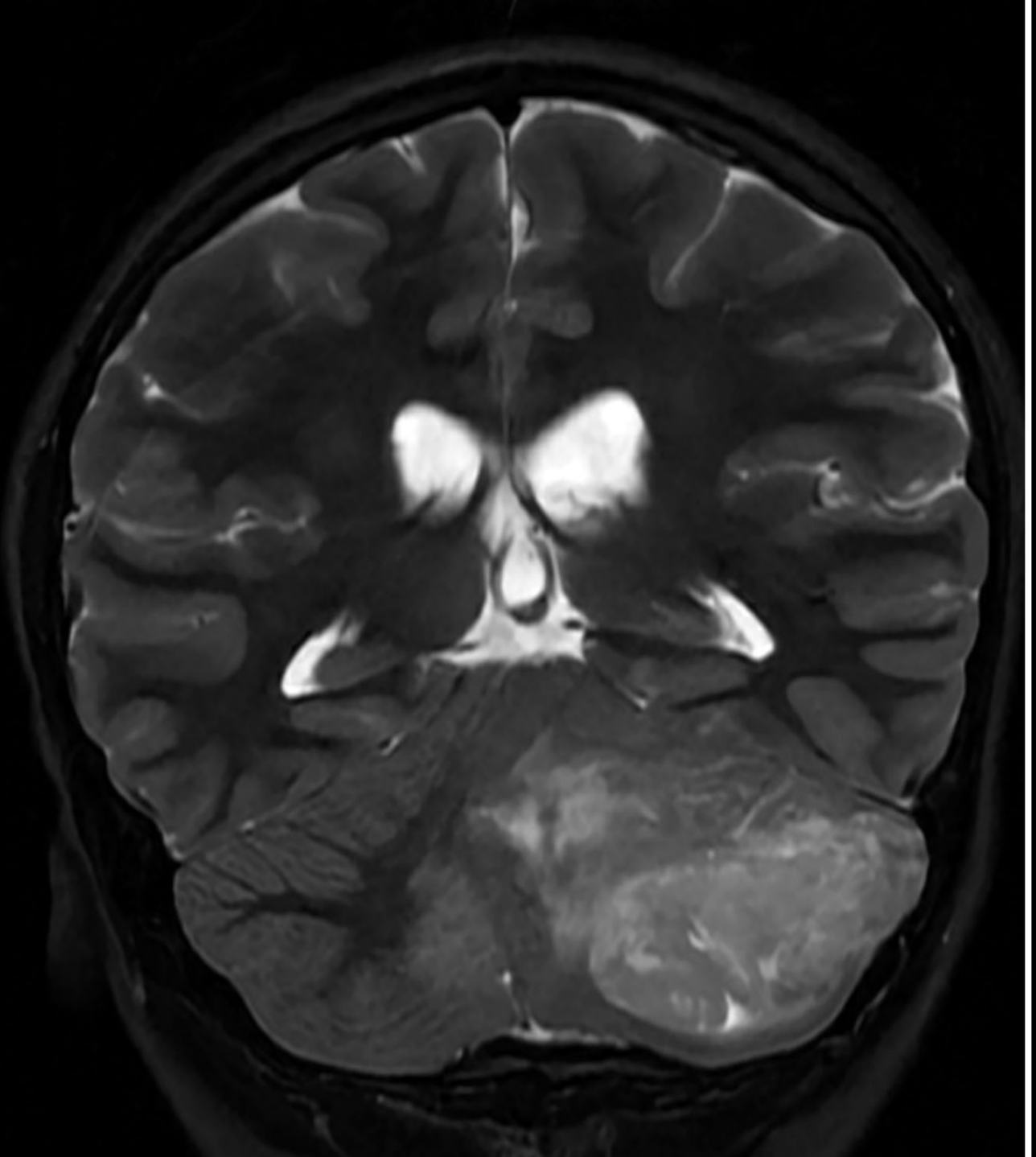
Mucocutaneous lesions[b]

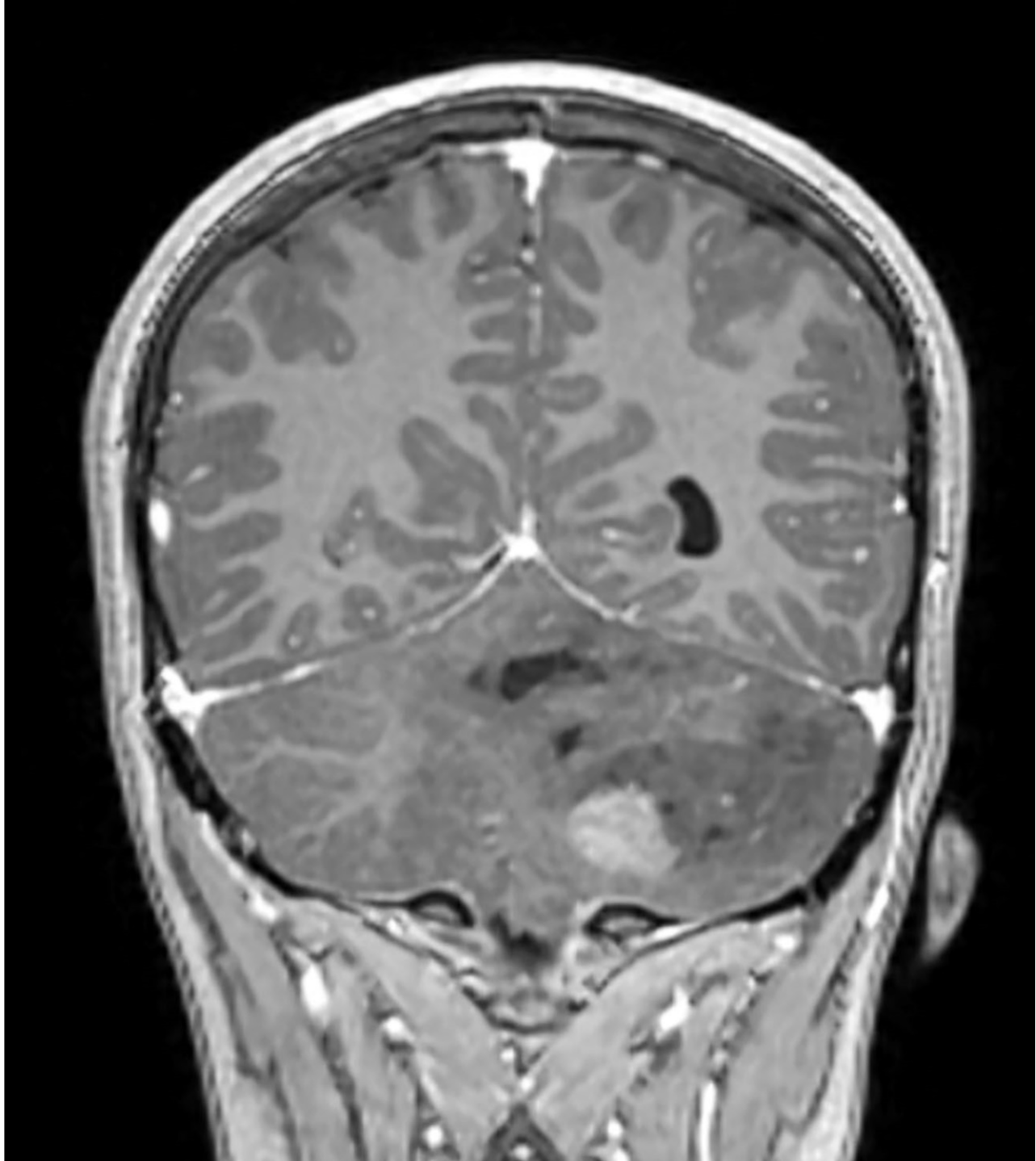
- One biopsy-proven trichilemmoma
- Multiple palmoplantar keratoses
- Multifocal cutaneous facial papules
- Macular pigmentation of the glans penis

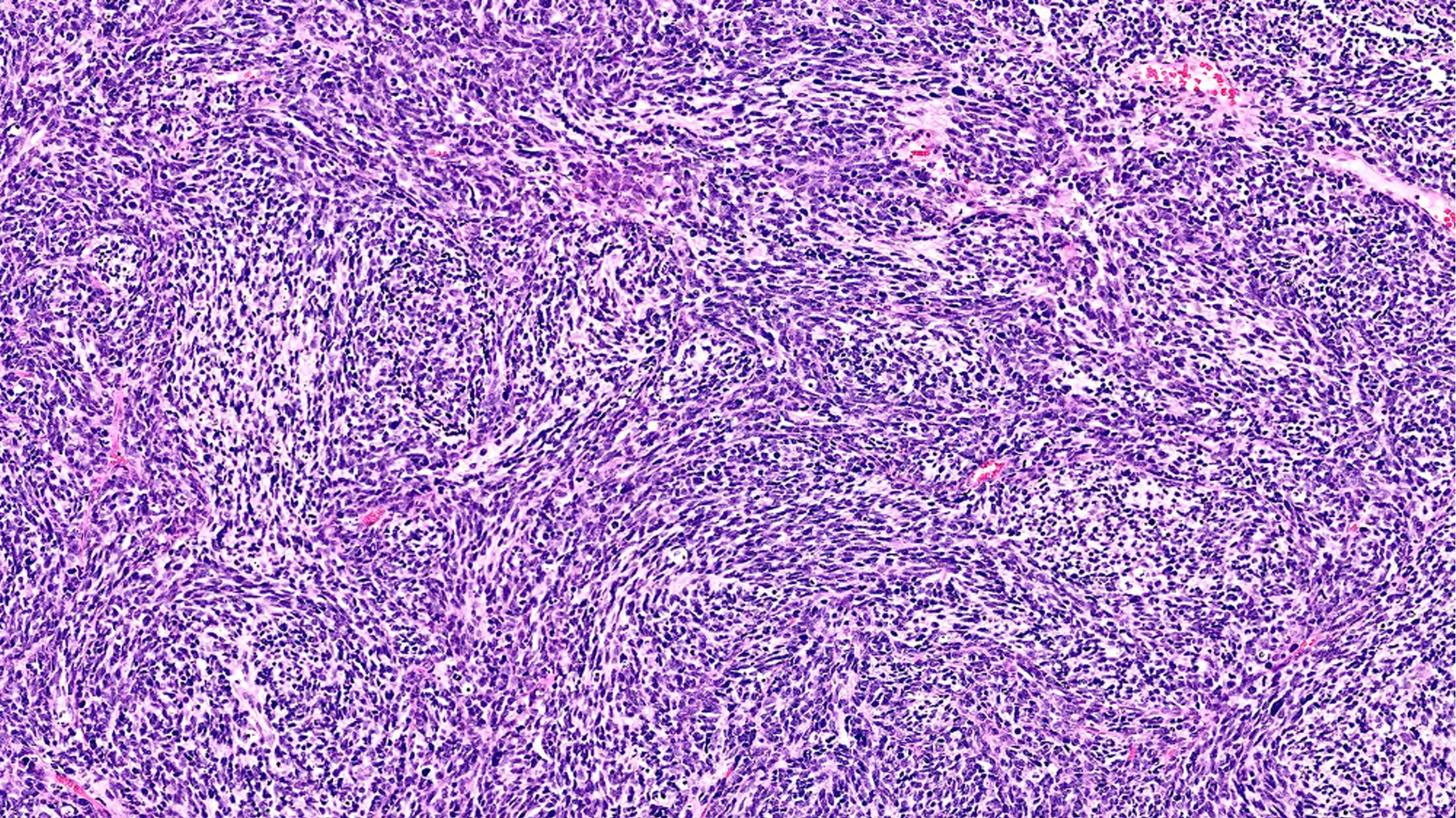
Multiple gastrointestinal hamartomas or ganglioneuromas[b]

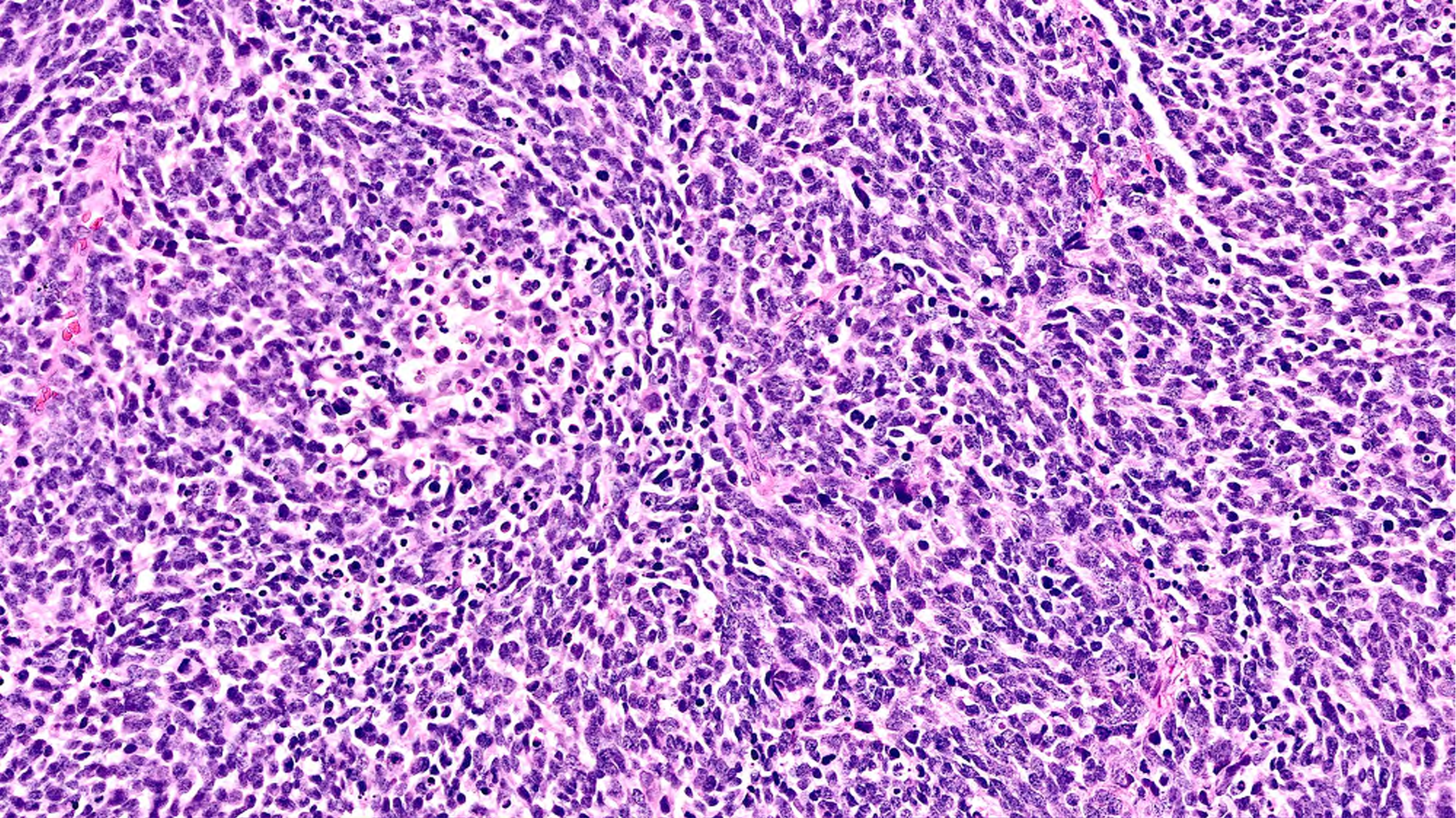
CASE 1

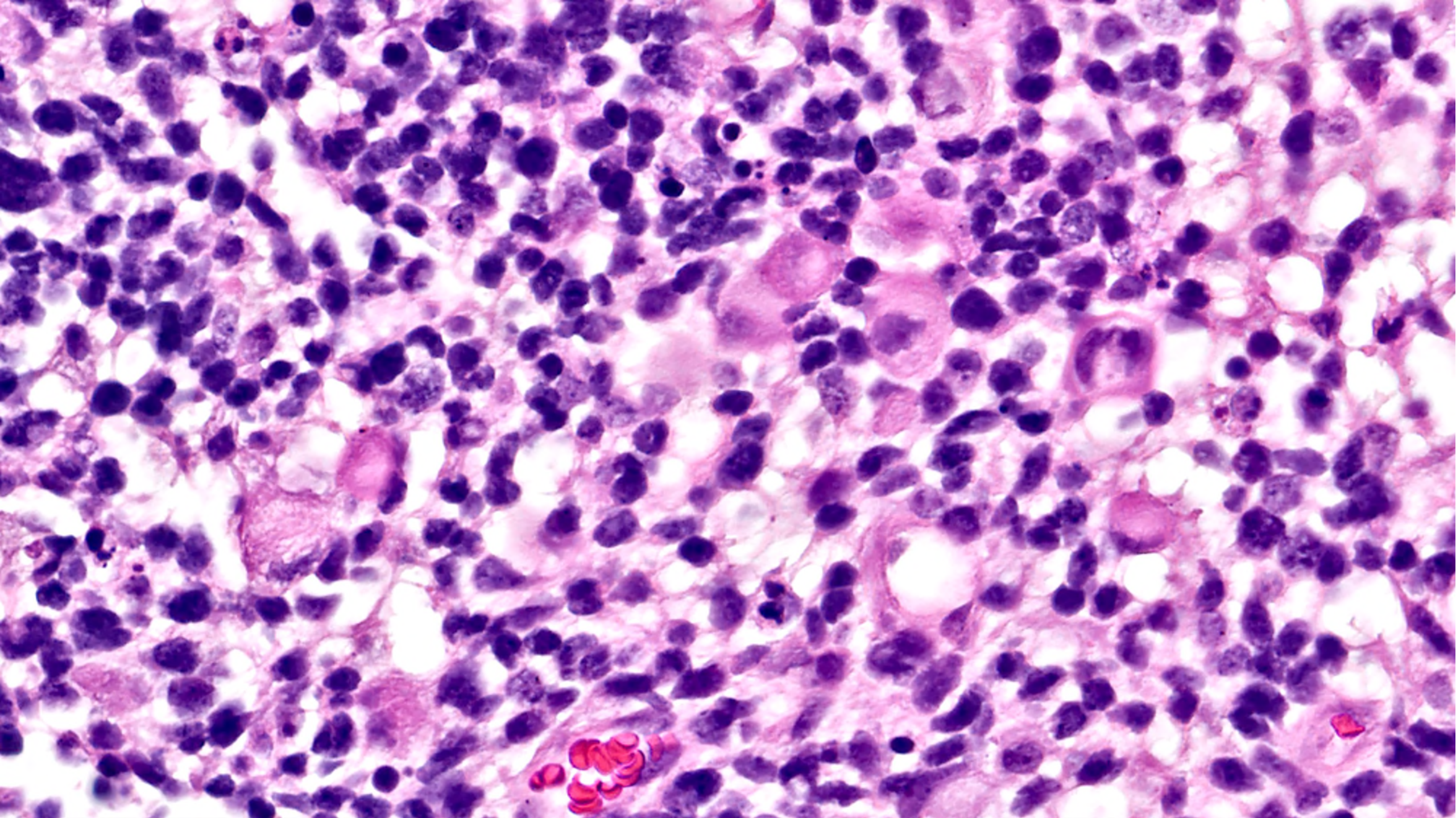
- 12-yo M with intermittent headaches for a year
- Diagnosed with migraines and treated with medication
- Suffered head trauma while playing sports
- Found to have papilledema on exam
- Neuroimaging: posterior fossa mass

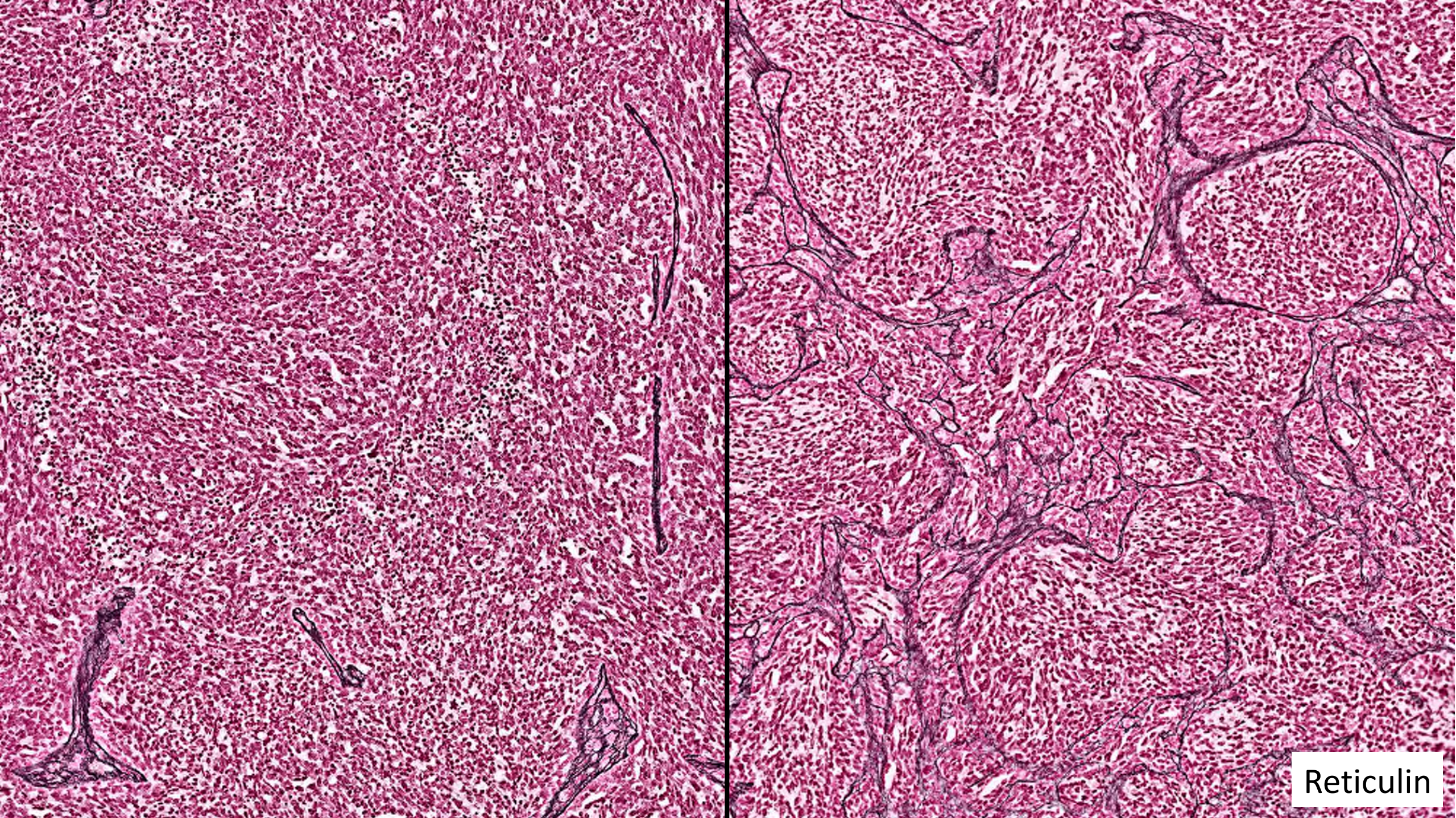


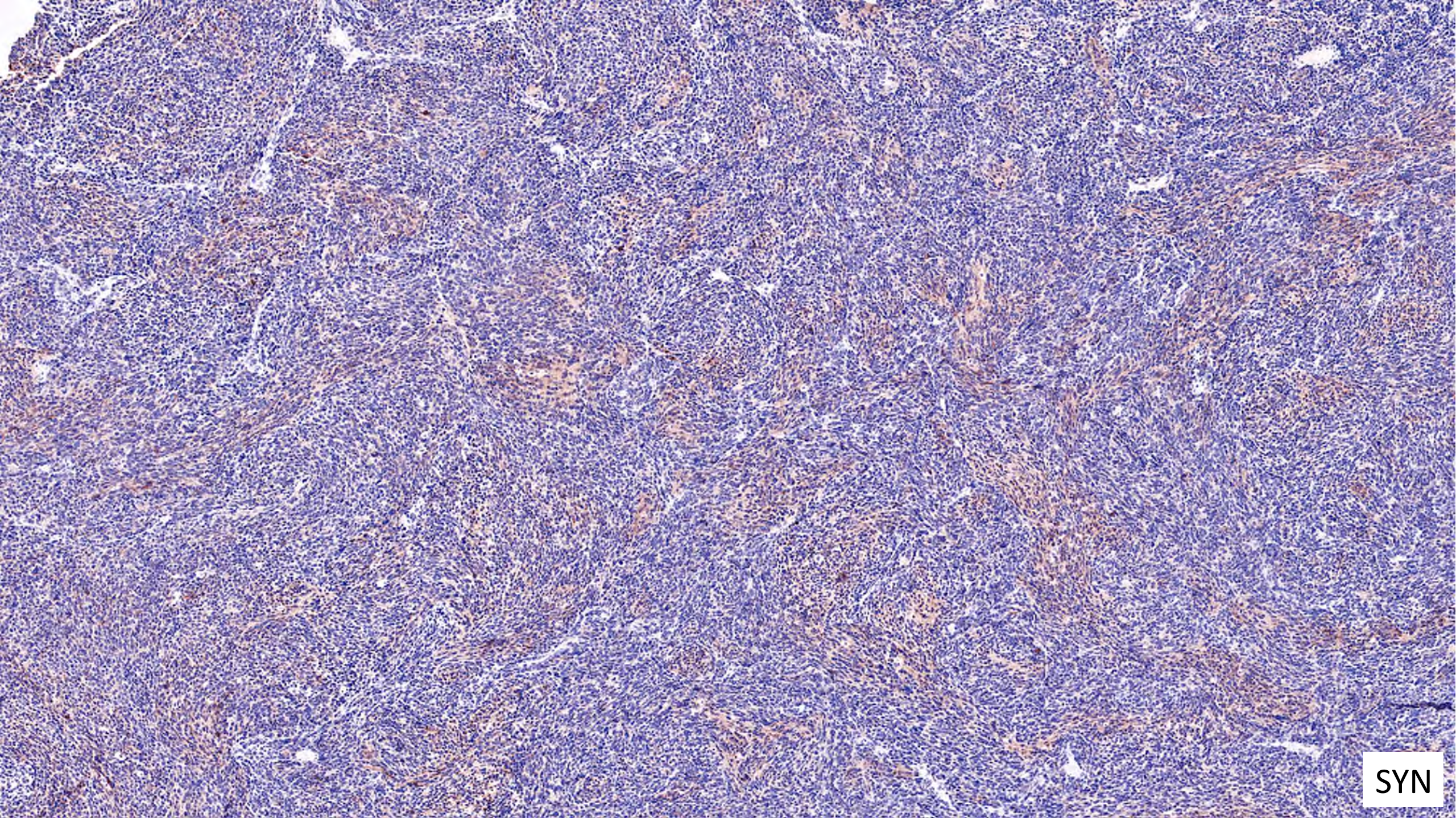


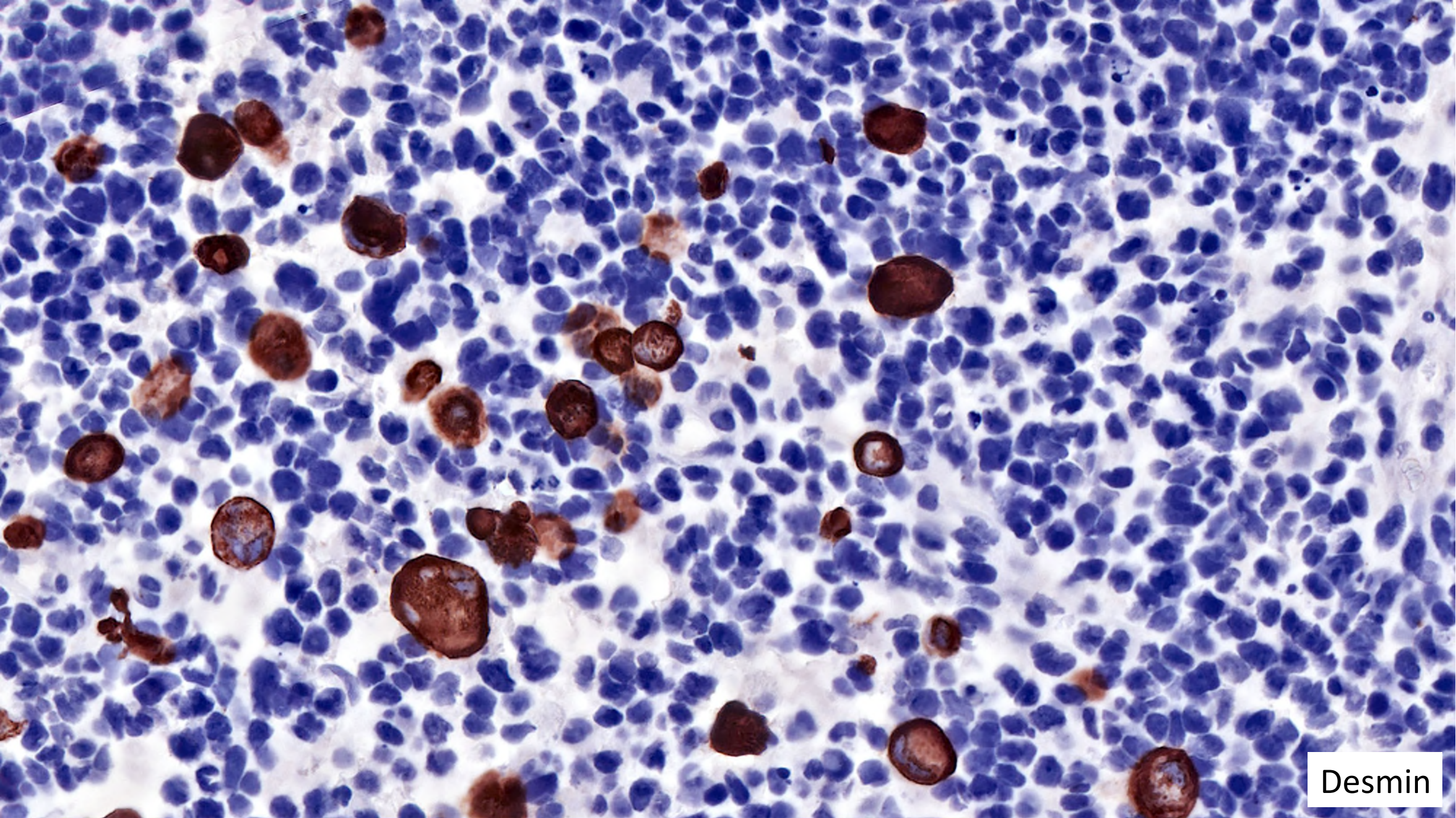


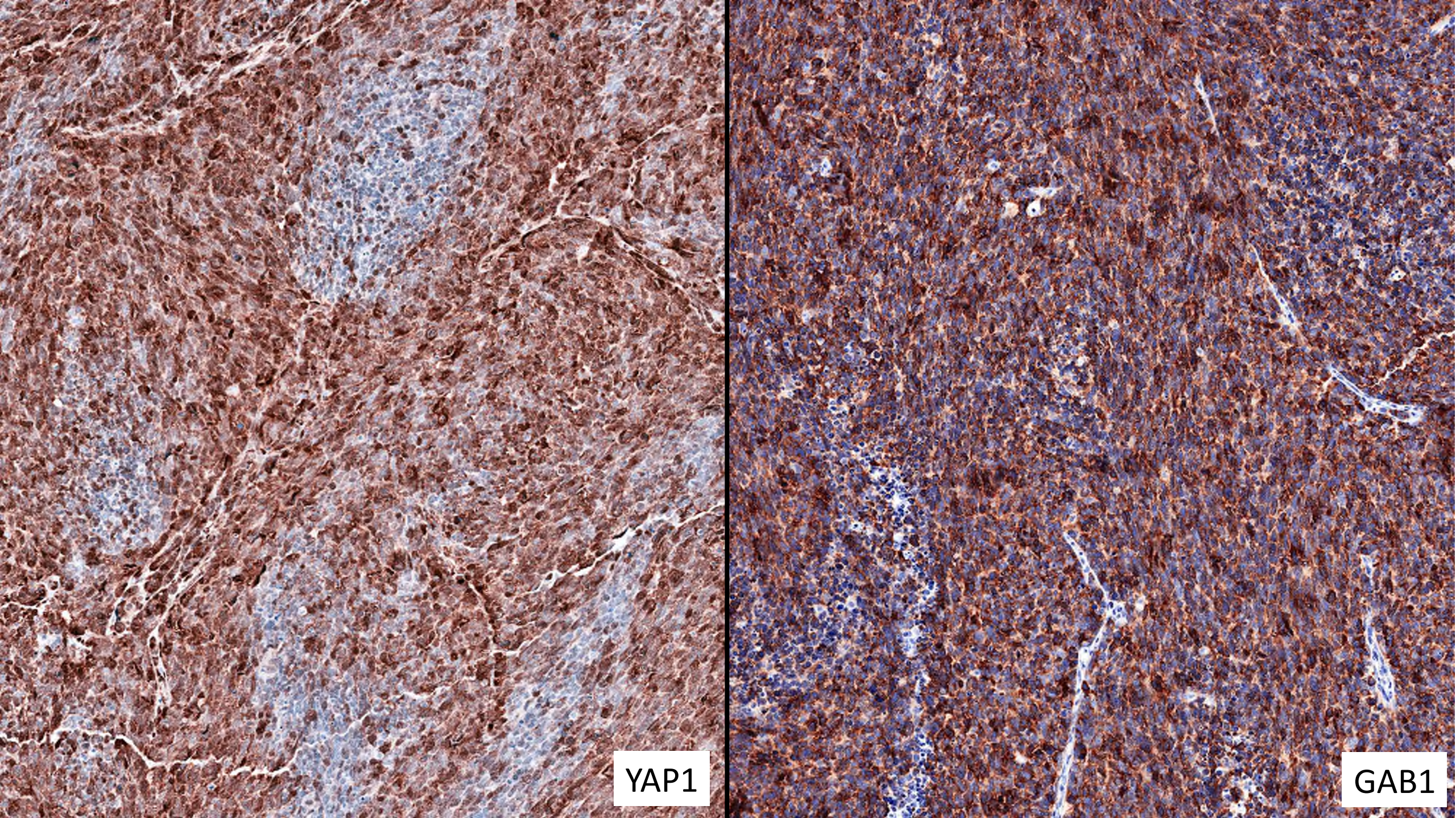


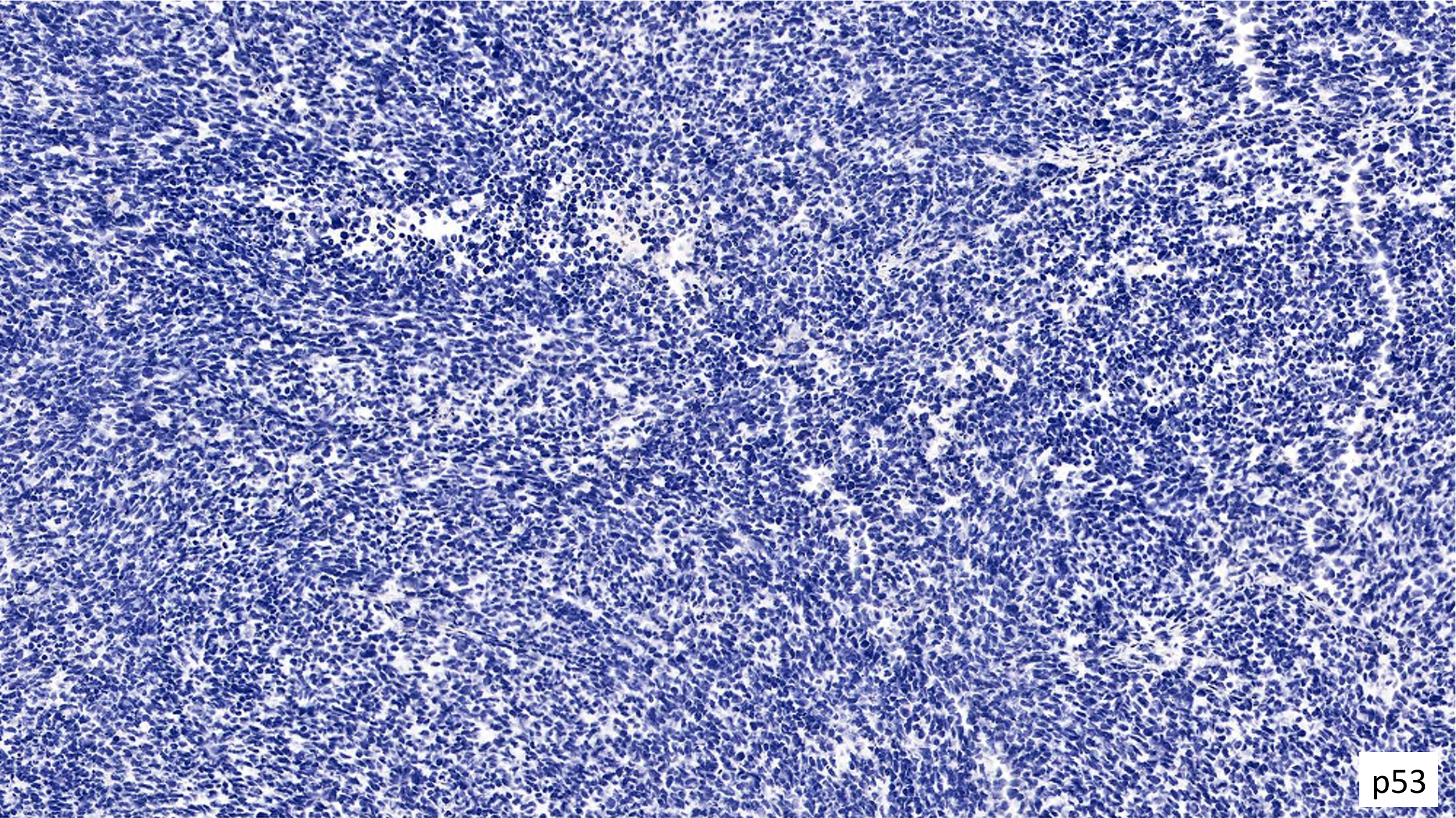



Reticulin


SYN


Desmin


YAP1
GAB1


p53

Initial Dx: Medulloblastoma, large cell/anaplastic histologic type with focal myogenic differentiation, SHH-activated and likely *TP53*-mutant molecular group, CNS WHO grade 4

- Recommend paired tumor/germline NGS and DNAM profiling studies

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
PRKCA p.R389*	NM_002737.2	Likely Pathogenic	488	26%

'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and 'Likely Pathogenic' classifications are based on CCGL molecular pathologist/geneticist interpretation of data from somatic and germline databases and published literature. Variants classified as 'Possibly Pathogenic' have unknown significance but occur in genes or molecular pathways known to be recurrently altered in the tumor type.

Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
TP53 p.T125= (c.375G>A, p.Thr125=)	NM_000546.5	Pathogenic	938/582	49%/98%

*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist/geneticist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Alterations in the normal samples are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

0 of 83 tested microsatellites (0.00%) were found to be unstable. This is interpreted as Microsatellite Stable (MSS).

Assessment of microsatellite instability (MSI) by percentage of unstable sites:
<20%: MSI absent (MSS) | 20-30%: MSI equivocal | >30%: MSI present (MSI-High)

UCSF500 tumor mutation burden: 0.7 mutations/Mb

INTERPRETATION

Sequencing of this medulloblastoma with large cell/anaplastic histologic features demonstrates a pathogenic mutation in TP53 that is present in the germline sample and shows selection in the tumor sequencing (49% and 98% allele frequency, respectively). This sequence change affects codon 125 of the TP53 mRNA. It is a 'silent' change, meaning that it does not change the encoded amino acid sequence of the TP53 protein. This variant also falls at the last nucleotide of exon 4 of the TP53 coding sequence, which is part of the consensus splice site for this exon. This variant is not present in population databases (ExAC no frequency). This variant has been reported in many individuals affected with Li-Fraumeni syndrome (PMID: 1467311, 11420676, 18511570, 21348412, 22170717, 9242456, 24382691, 25945745, 27501770) and adrenocortical carcinoma (PMID: 22170717, 25584008) and was reported to segregate with TP53-related cancers in two of these families (PMID: 1467311, 9242456). ClinVar contains an entry for this variant (Variation ID: 177825). Experimental studies have shown that this variant results in altered TP53 mRNA splicing that will likely result in an absent or non-functional protein product (PMID: 1467311, 11420676). For these reasons, this variant has been classified as Pathogenic. Referral to genetic counseling is recommended to further explore the future cancer risk to this patient and patient's family. Also identified is an inactivating nonsense mutation in the PKC alpha protein PRKCA, which is a member of the AGC (PKA, PKG, PKC) family of cytoplasmic serine/threonine kinases.

Copy number analysis reveals several large scale chromosomal changes including gains of distal 4q, distal 7q, chromosome 8, distal 13q, distal 15q, and losses of 1p, distal 2q, 3p, 10q, 11q, 12p, most of 13q, 14q, chromosome 16, distal 17p (including TP53) chromosome 18, and 20p.

Brain tumor methylation classifier results [1]

Methylation classes

	Calibrated Score
methylation class family Medulloblastoma, SHH	1
methylation class medulloblastoma, subclass SHH A (children and adult)	1

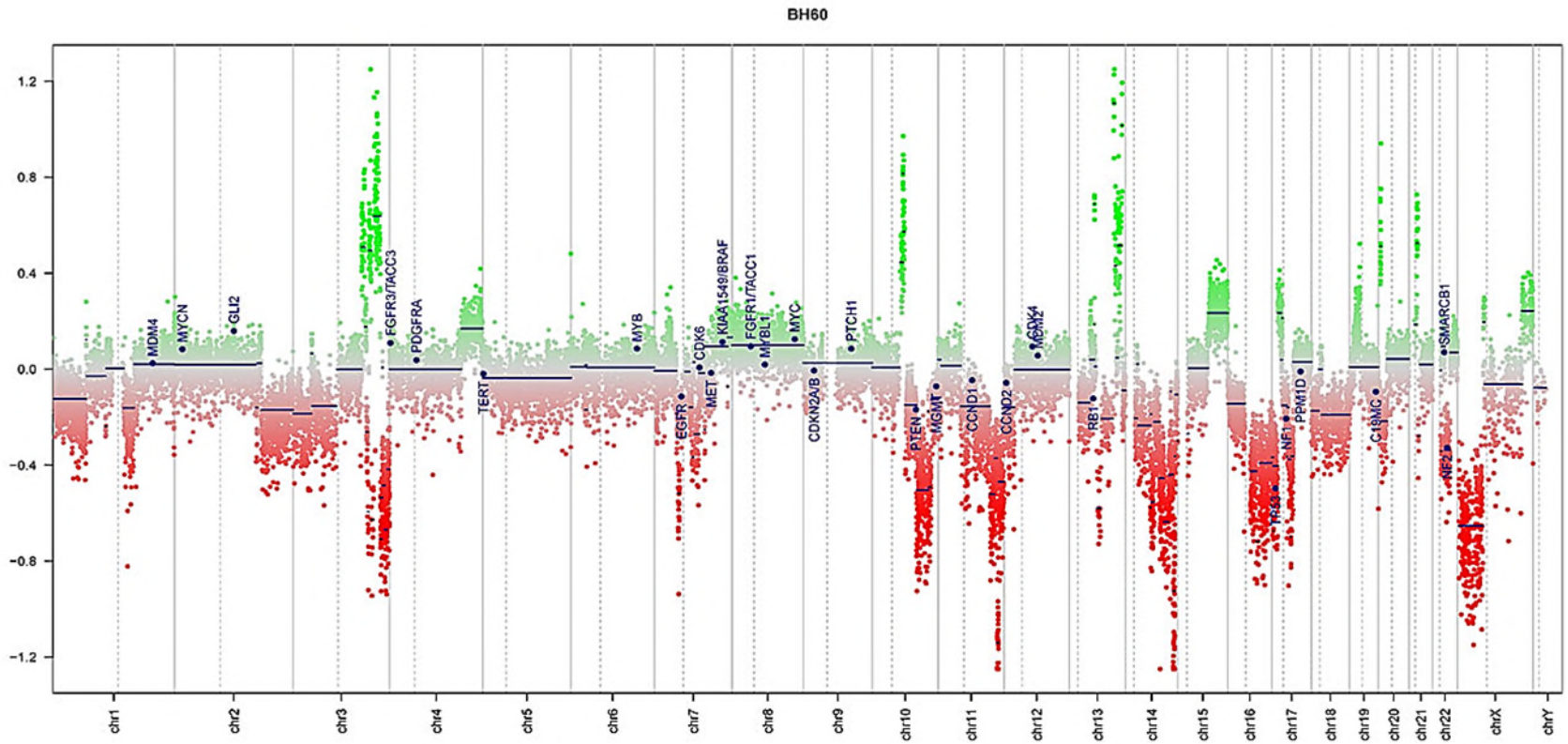
Methylation Classes and Families are reported only for results with score >= 0.3. Indented lines in the table are family members with score >= 0.1.

Methylation Class Description

methylation class family Medulloblastoma, SHH: The methylation class family Medulloblastoma, SHH comprises the methylation classes methylation class medulloblastoma, subclass SHH A (children and adult), methylation class medulloblastoma, subclass SHH B (infant).

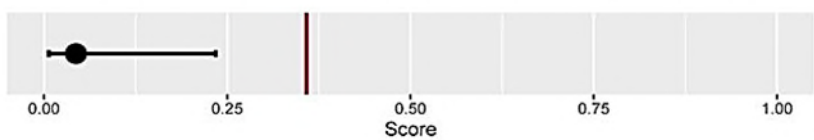
methylation class medulloblastoma, subclass SHH A (children and adult): The methylation class medulloblastoma, subclass SHH A (children and adult) is comprised of tumors diagnosed as Medulloblastoma, genetically defined, SHH-activated occurring in non-infant patients. Histologically most cases fall into the desmoplastic variant, sometimes classic and occasionally large cell/anaplastic groups. Tumors are located in the cerebellum, usually laterally. Median age is 22 years (range 3 to 51). Upstream SHH pathway alterations (i.e. PTCH1 and SMO) are relatively common. Importantly, this methylation class also includes the majority of TP53-mutated SHH tumors (often Li-Fraumeni associated), which typically occur in children (~8-16 years) and often have large cell/anaplastic morphology, with dramatic copy number alterations (chromothripsis).

Copy Number Variation Profile [2]



Depiction of chromosome 1 to 22 (and X/Y if automatic prediction was successful). Gains/amplifications represent positive, losses negative deviations from the baseline. 29 brain tumor relevant gene regions are highlighted for easier assessment.

MGMT promoter methylation status prediction [3]



Status	Estimated	CI_Lower	CI_Upper	Cutoff
unmethylated	0.044	0.007	0.234	0.358

References

1. Capper D, Jones DTW, Sill M, Hovestadt V et al., Nature. 2018 Mar 22;555(7697):469-474.
2. Hovestadt & Zapatka, http://www.bioconductor.org/packages/devel/bioc/html/conumee.html)
3. Bady et al, J Mol Diagn 2016; 18(3):350-61).

Final Dx: Medulloblastoma, large cell/anaplastic histologic type with focal myogenic differentiation, SHH-activated and *TP53*-mutant molecular group, CNS WHO grade 4, arising in the setting of Li-Fraumeni syndrome

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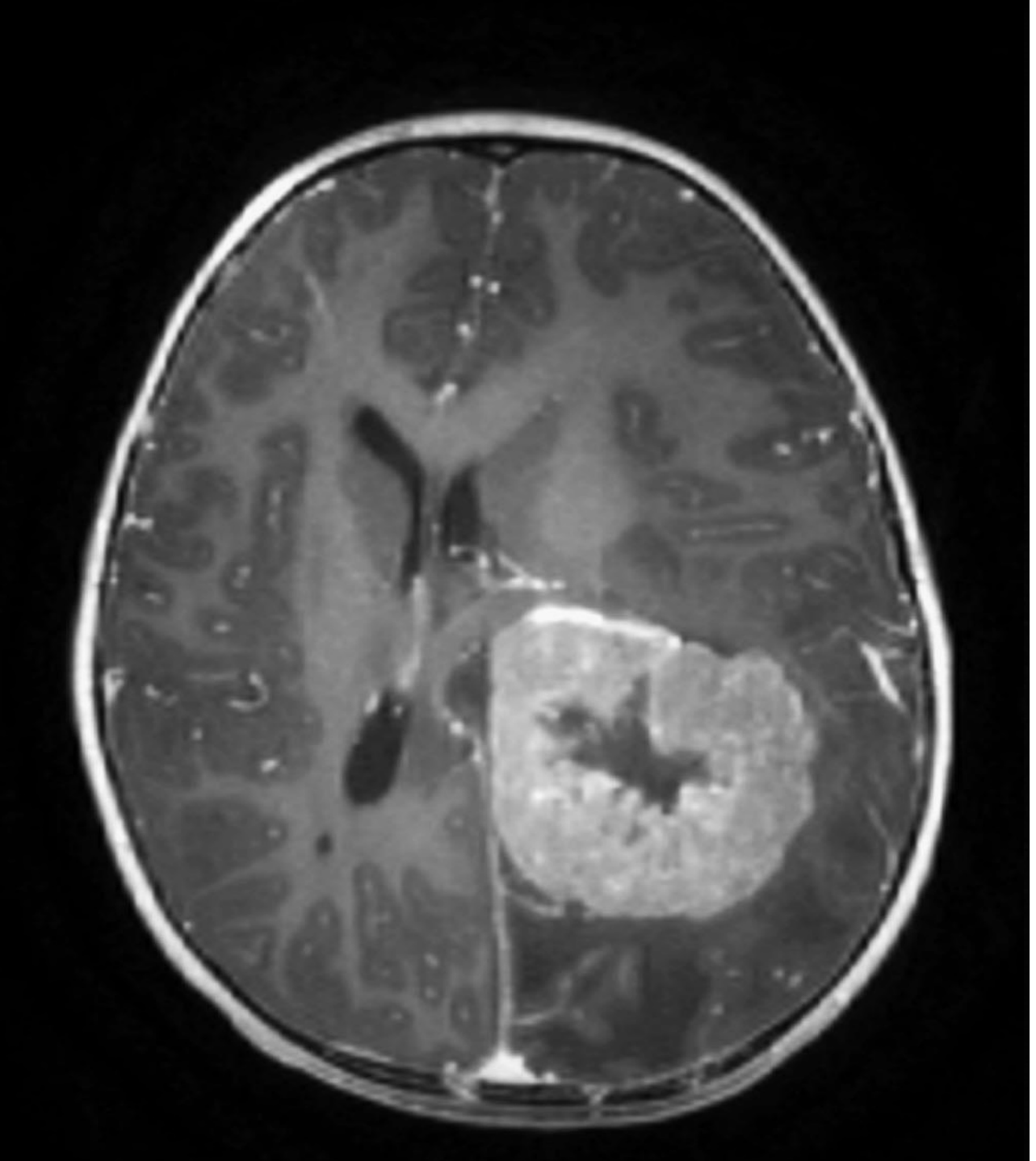
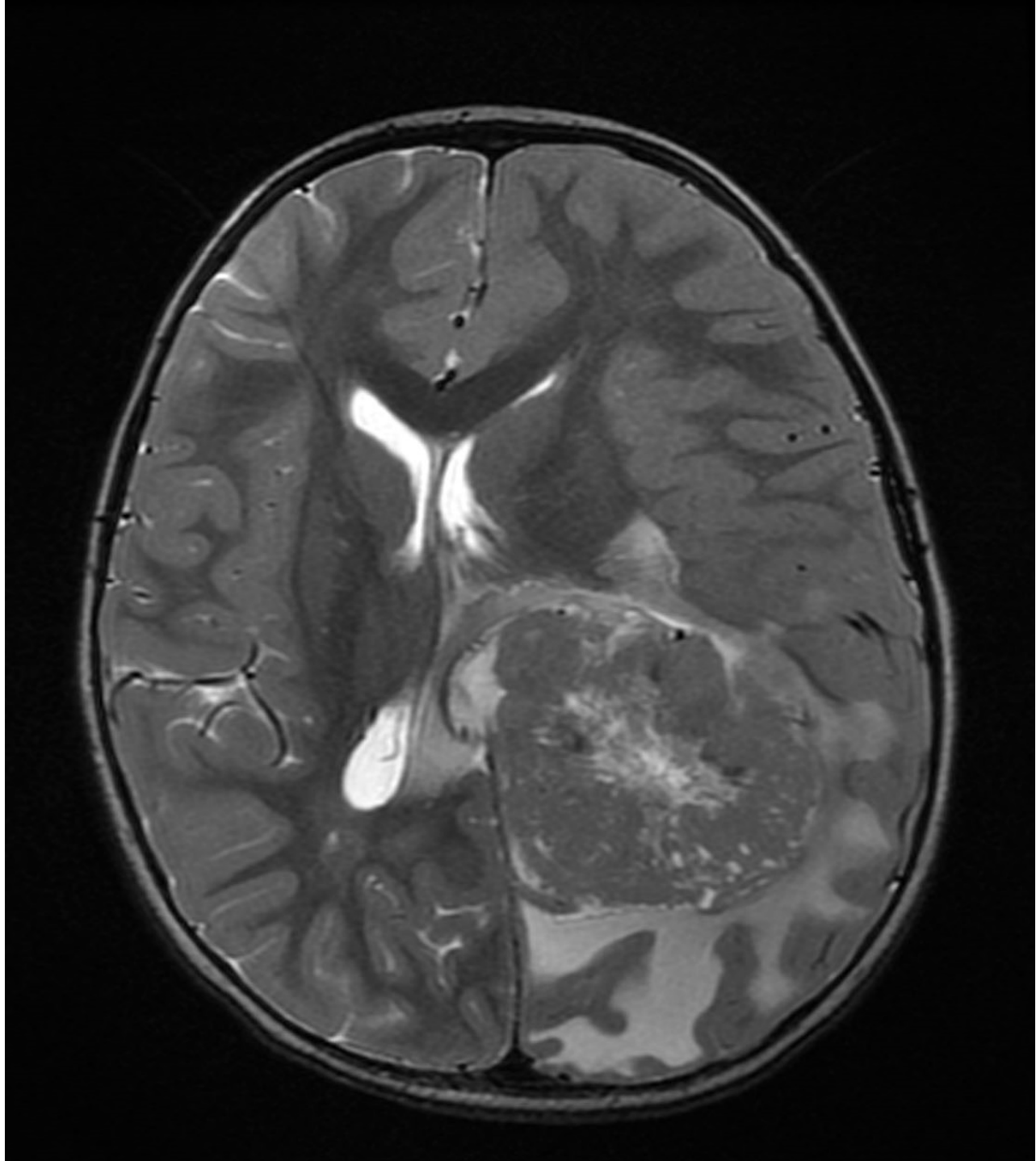
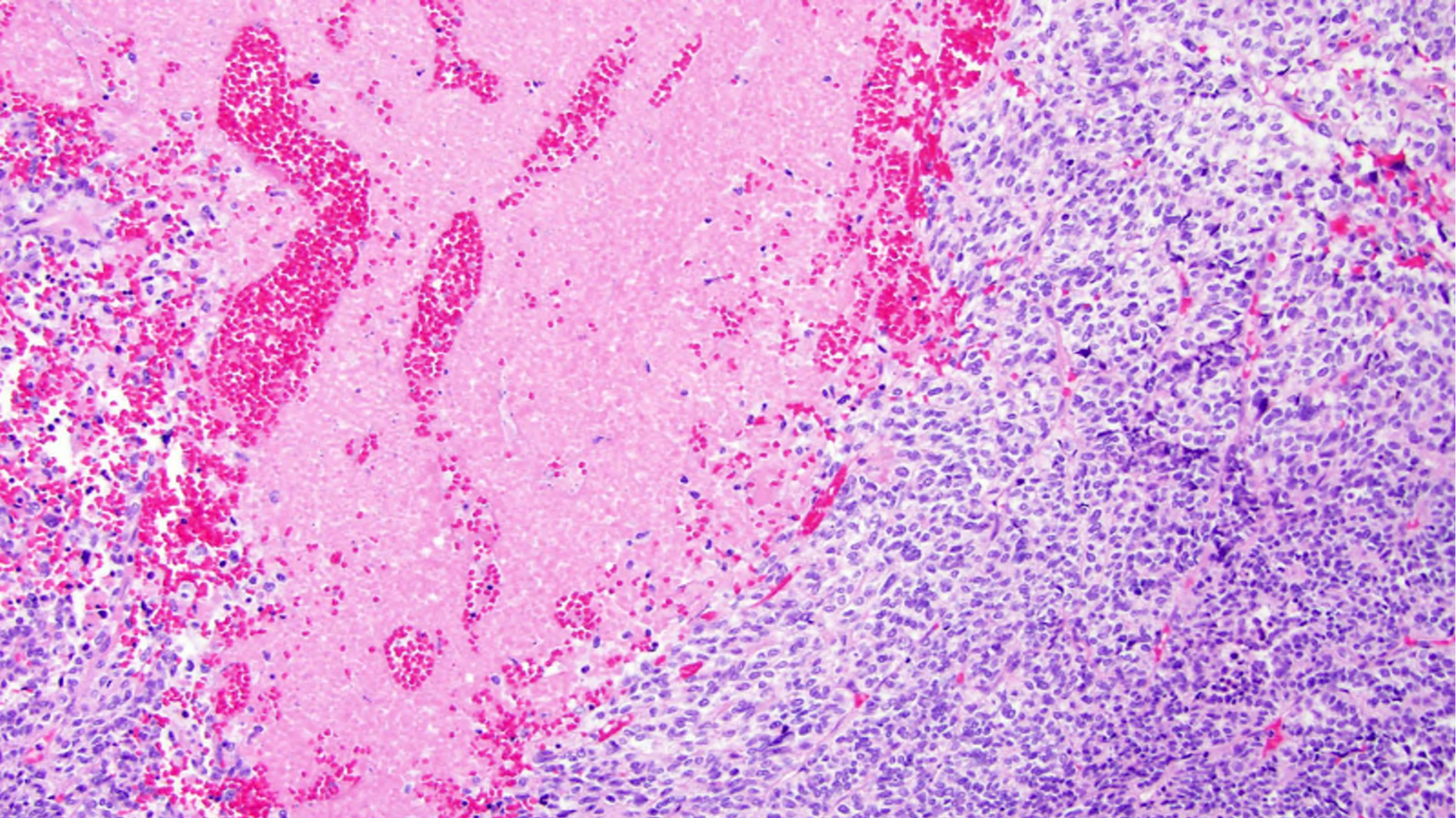
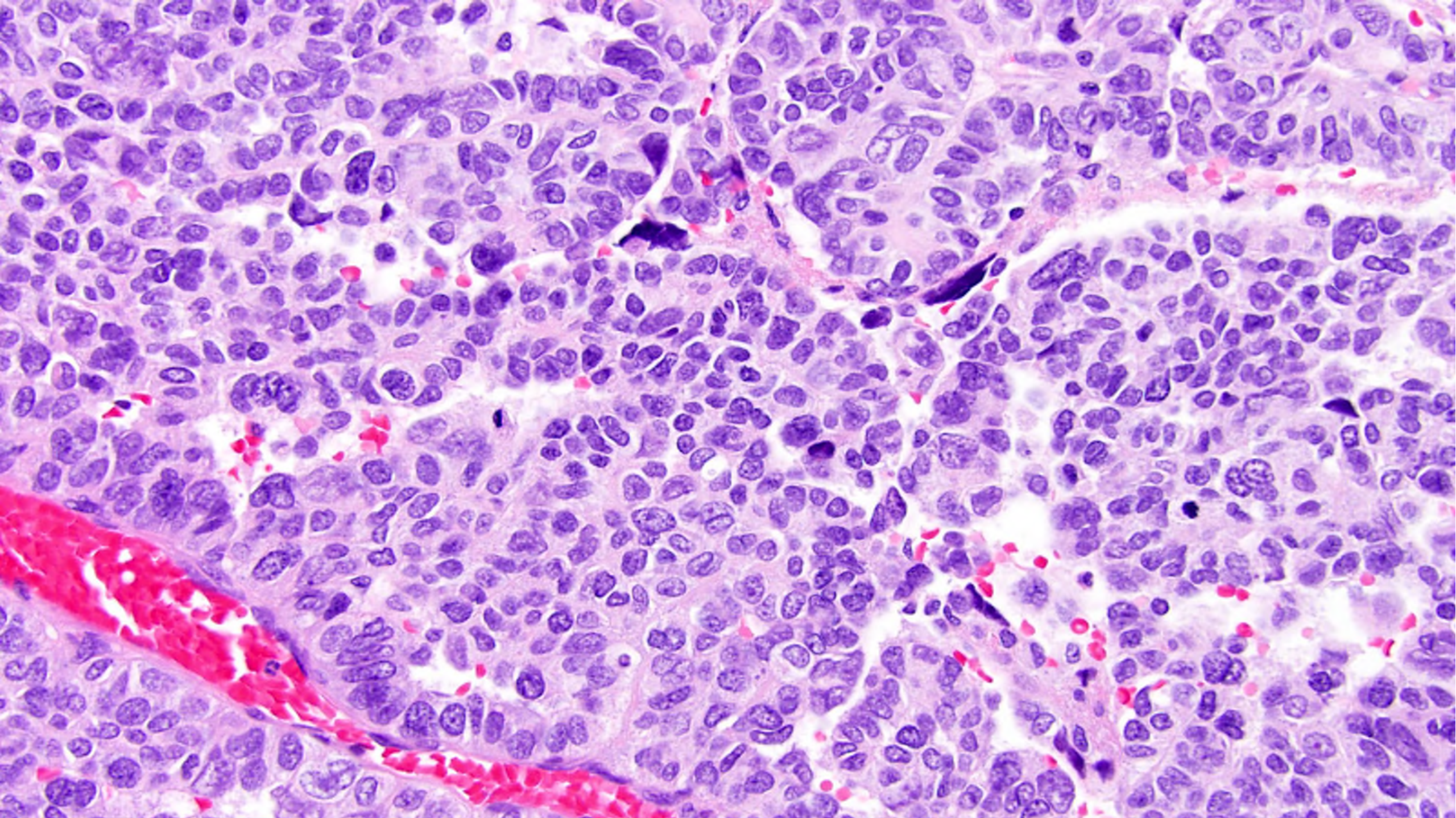
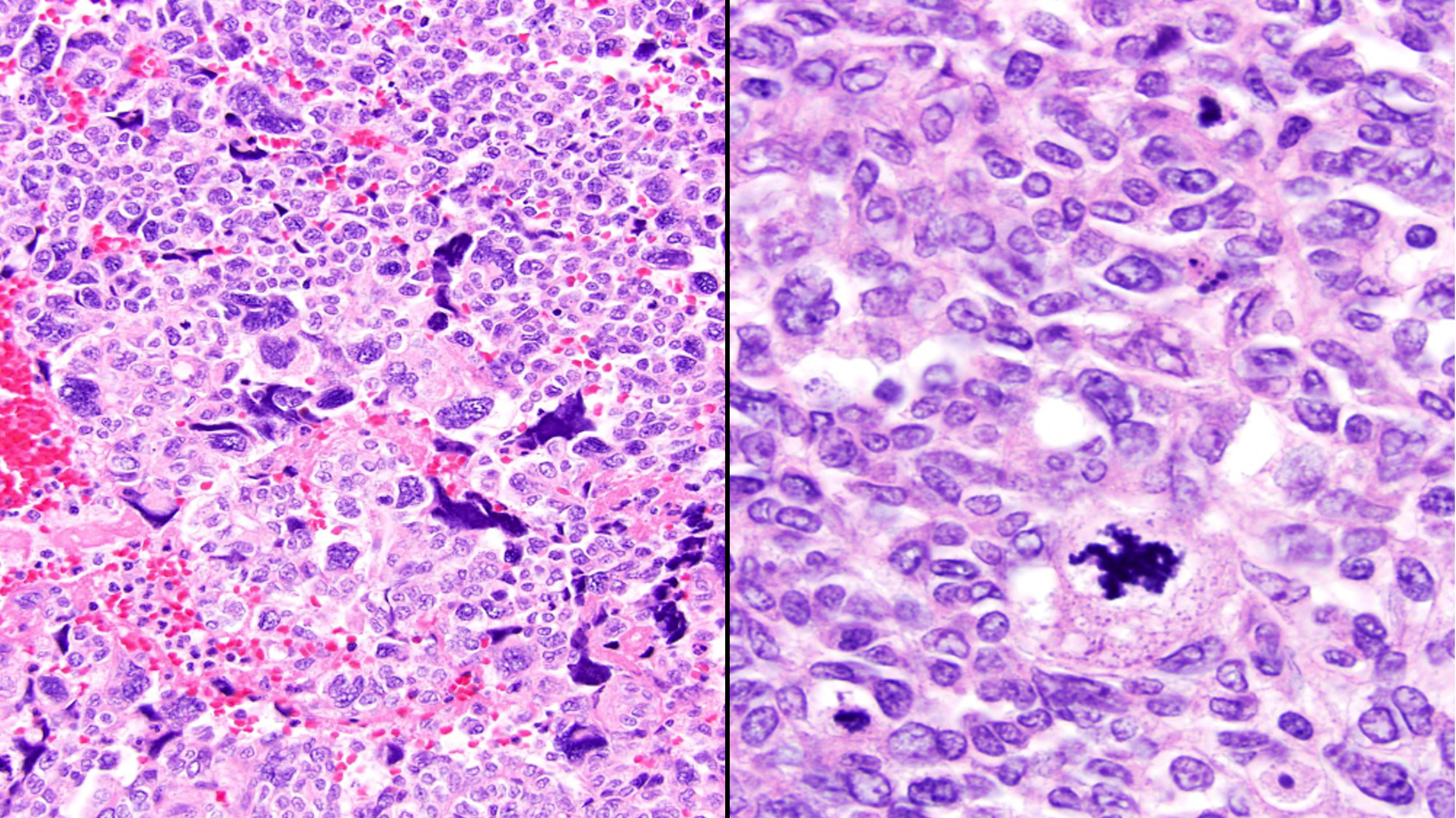
CASE 2

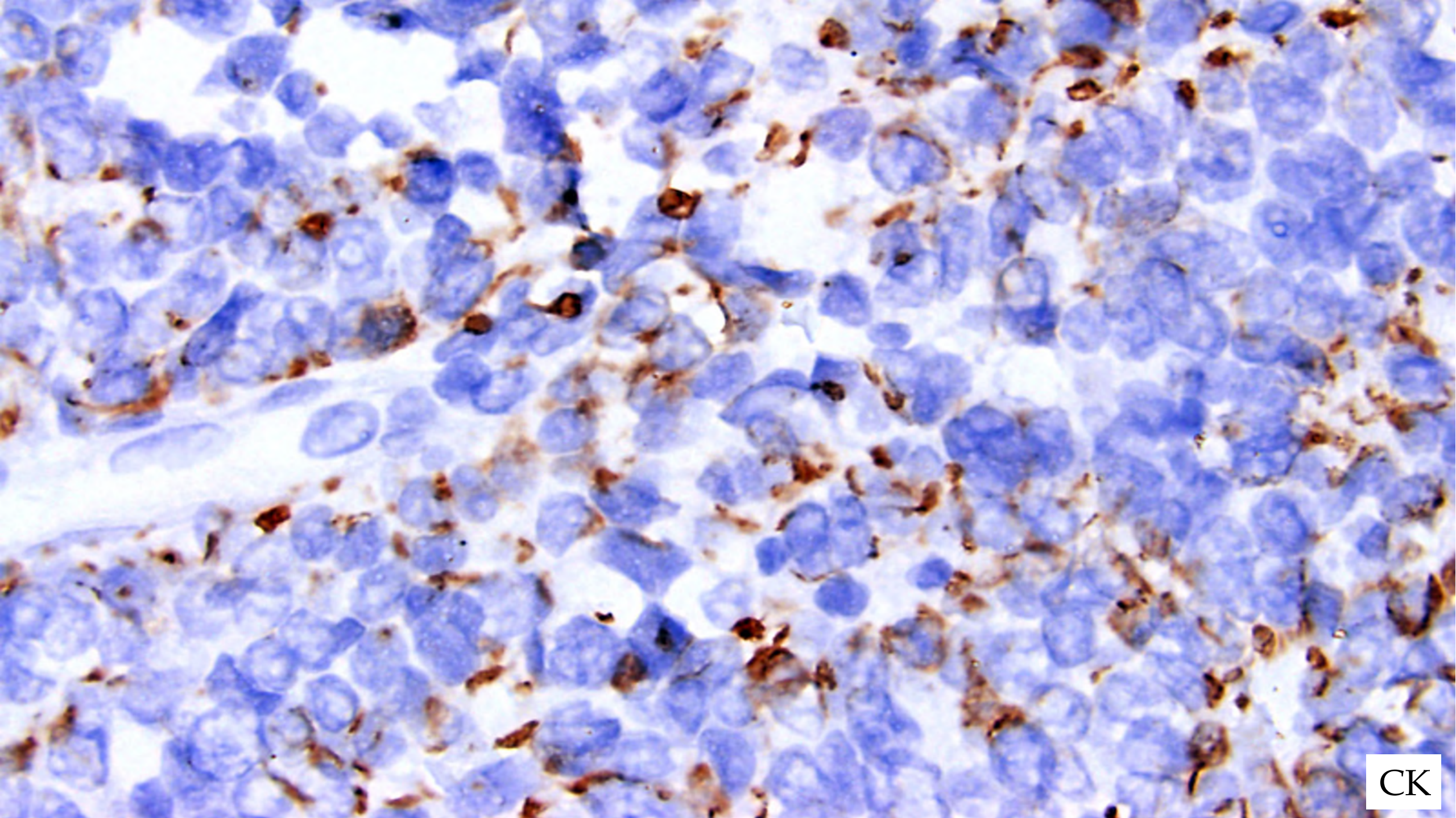
- 3-yo boy with no significant past medical history
- Presented to local ED in status epilepticus
- MRI: 6 cm left-sided contrast enhancing intracranial mass

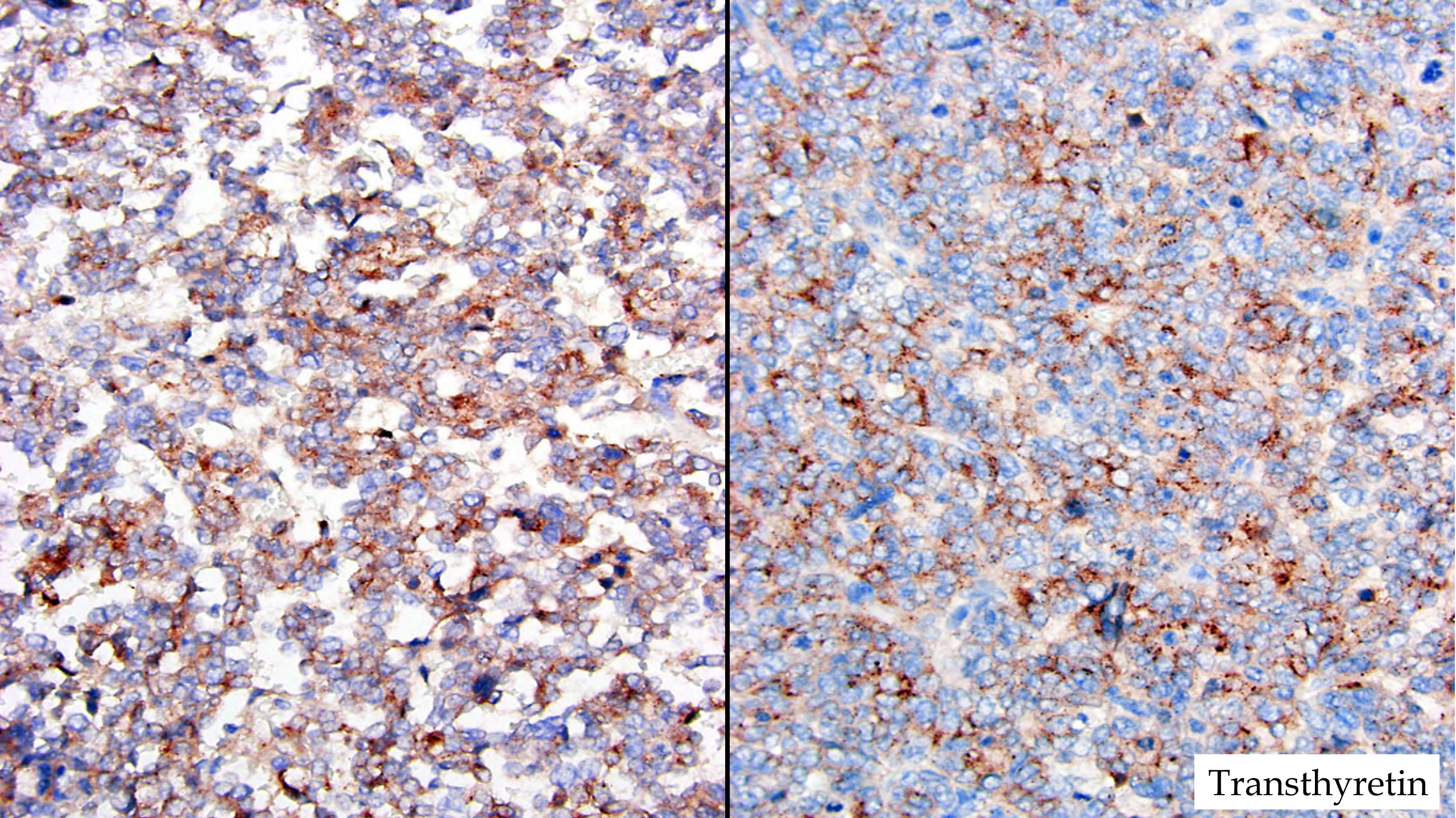



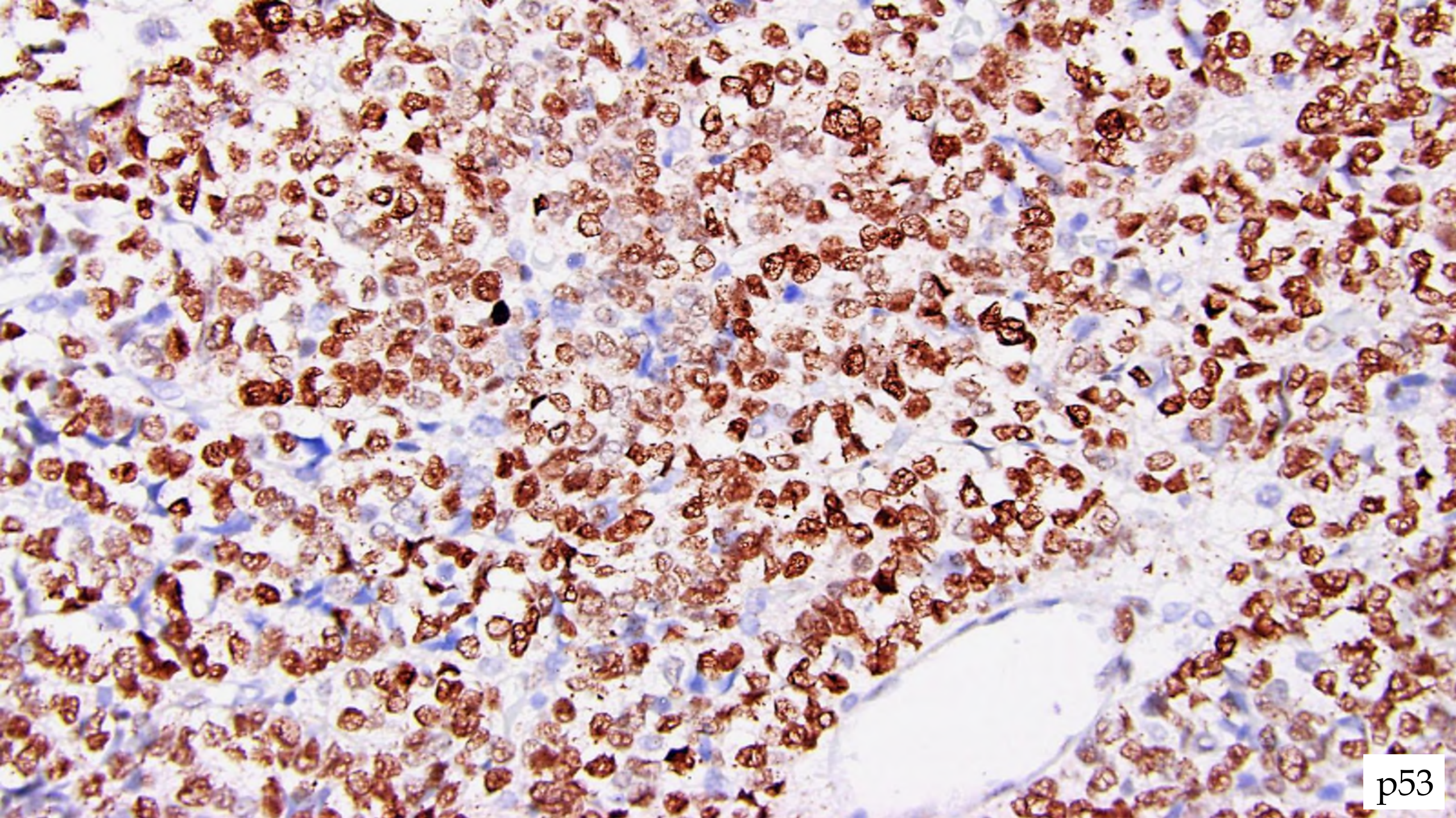







CK


Transthyretin


p53

UCSF500 NGS

GENOMIC ALTERATIONS IN THE TUMOR SAMPLE				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**COVERAGE**	**MUTANT ALLELE FREQUENCY**
TP53 p.M246V	NM_000546	Pathogenic	343	95%

'Coverage' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

GENOMIC ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**COVERAGE**	**MUTANT ALLELE FREQUENCY**
TP53 p.M246V	NM_000546	Pathogenic	348	47%
MSH6 p.T716fs	NM_000179	Pathogenic	775	49%

***Germline variants are only reported if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist.**

INTERPRETATION

Choroid plexus carcinoma is rare childhood tumor that is associated with germline TP53 mutations in a subset of cases (1-2), but the additional genetic alterations which drive these tumors are not well characterized (3).

This case shows two pathogenic germline mutations, a missense mutation in TP53 and a frameshift mutation in MSH6. The TP53 mutation shows loss of heterozygosity in the tumor and has been previously reported in both sporadic cancers and patients with Li-Fraumeni syndrome (4). The MSH6 variant is only seen at 4% mutant allele frequency in the tumor sample, which is consistent with reads coming from contaminating normal cells, and does not suggest that MSH6 is a driver of this tumor. Genetic counseling is recommended based on the presence of these two germline variants.

Numerous copy number changes are present including gains of chromosomes 1, 5, 8p, 10, 12, 13q, 14, 17q, X, and distal 3p and 3q. Losses are present in chromosomes 2, 4, 6, 7, 9, 11, 13p, 15, 16, 17p, 18, 19, 20, 21, 22, and interstitial 3p and 3q.

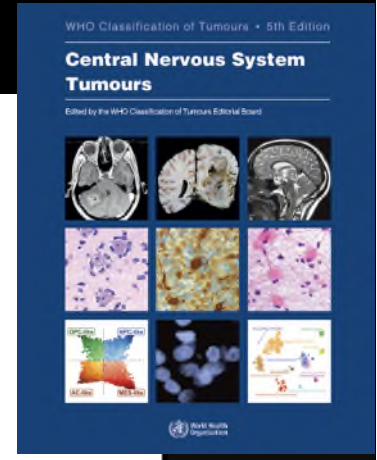
References:

1. Gozali AE, et al. Choroid plexus tumors; management, outcome, and association with the Li-Fraumeni syndrome: the Children's Hospital Los Angeles experience, 1991-2010. *Pediatr Blood Cancer* 58: 905-9, 2012.

Final Dx: Choroid plexus carcinoma, CNS WHO grade 3, arising in the setting of Li-Fraumeni syndrome

Patient Rx'd with chemo, but radiation withheld due to LFS. Neither parent had *TP53* mutation, but father had *MSH6* mutation, c/w Lynch syndrome. Combo presumed due to low level genetic instability in father, leading to germ cells with several de novo point mutations, including *TP53*

Li-Fraumeni Syndrome (*TP53* gene)

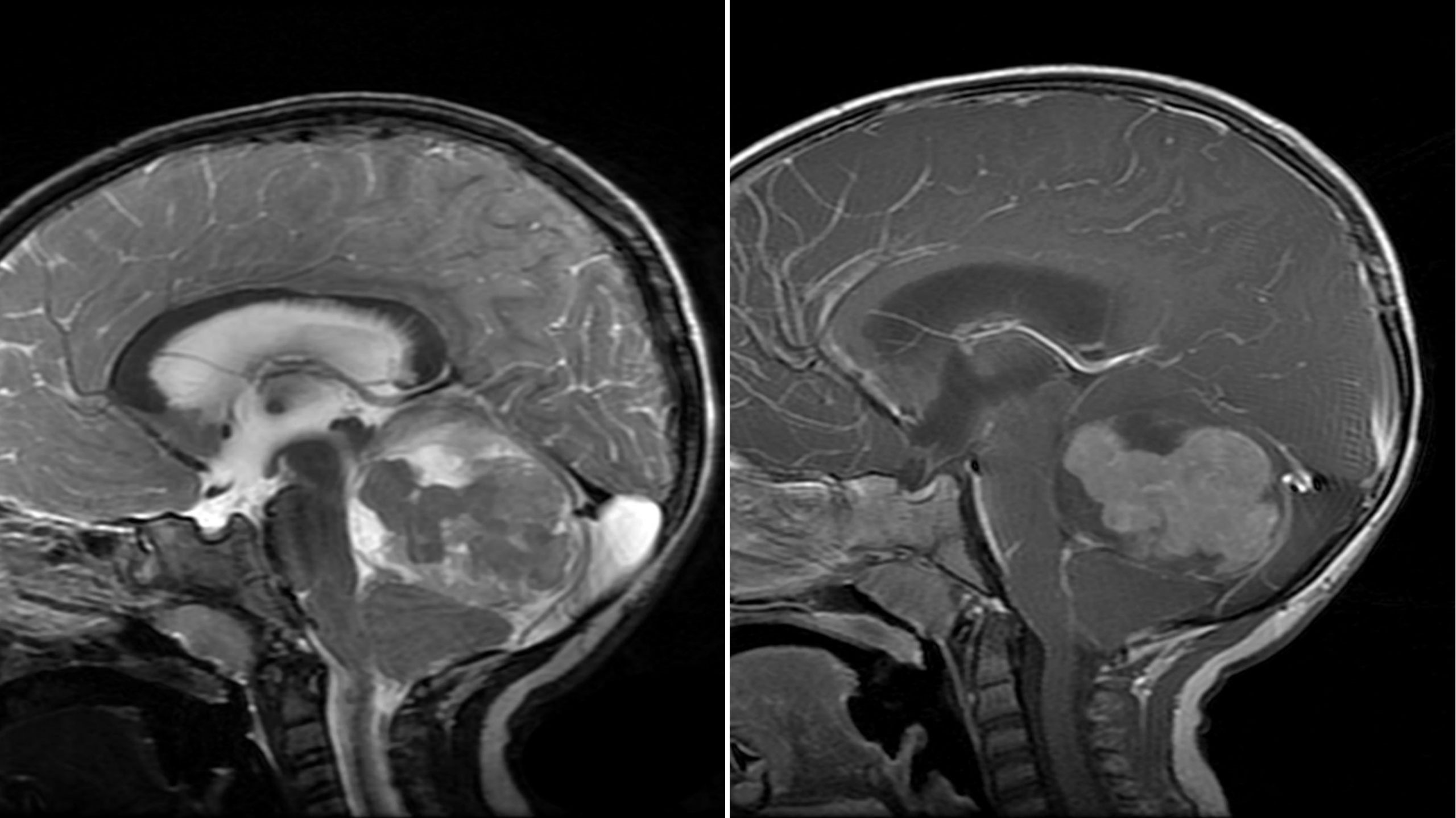


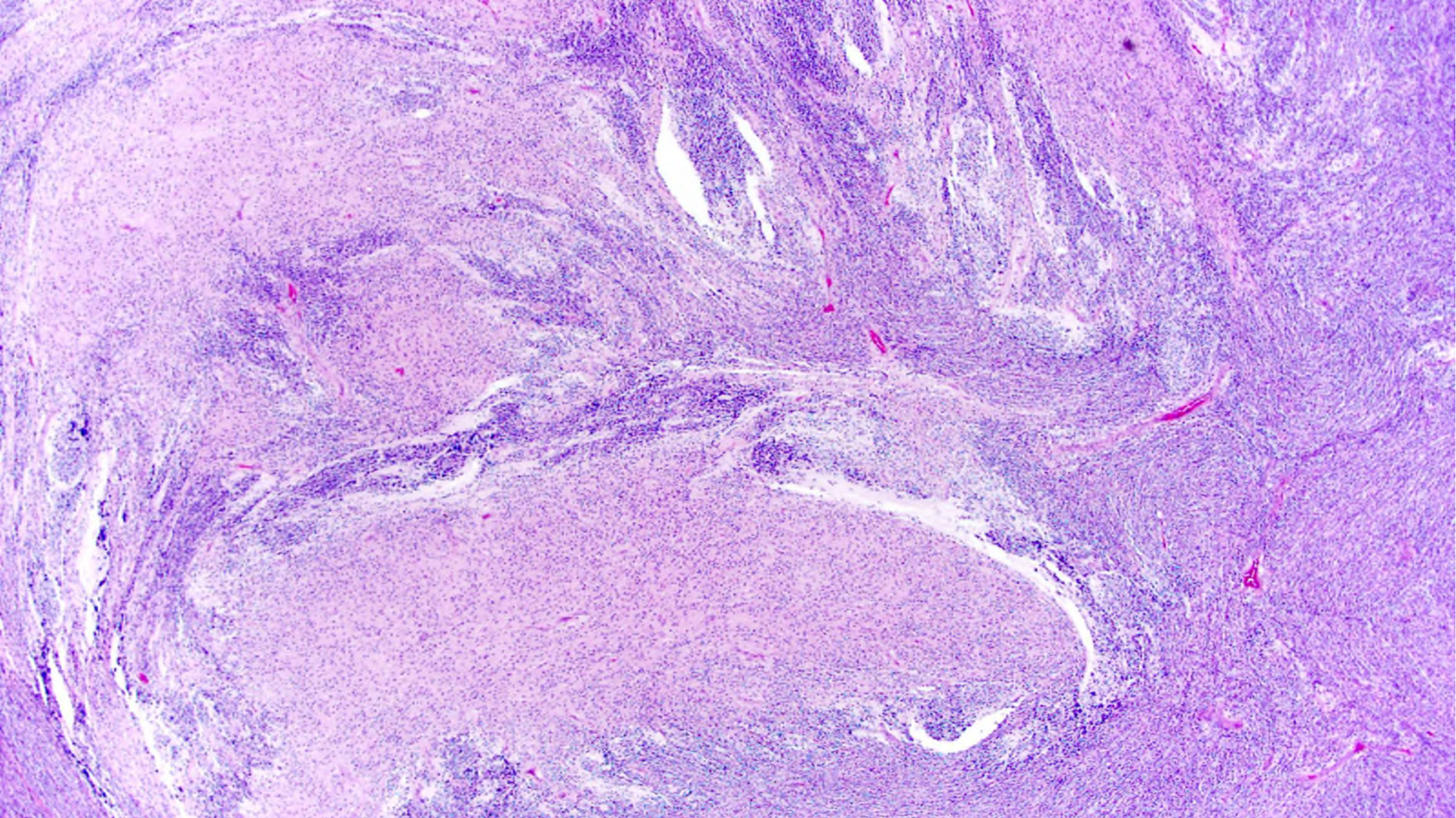
Brain Tumors Associated with Li-Fraumeni Syndrome

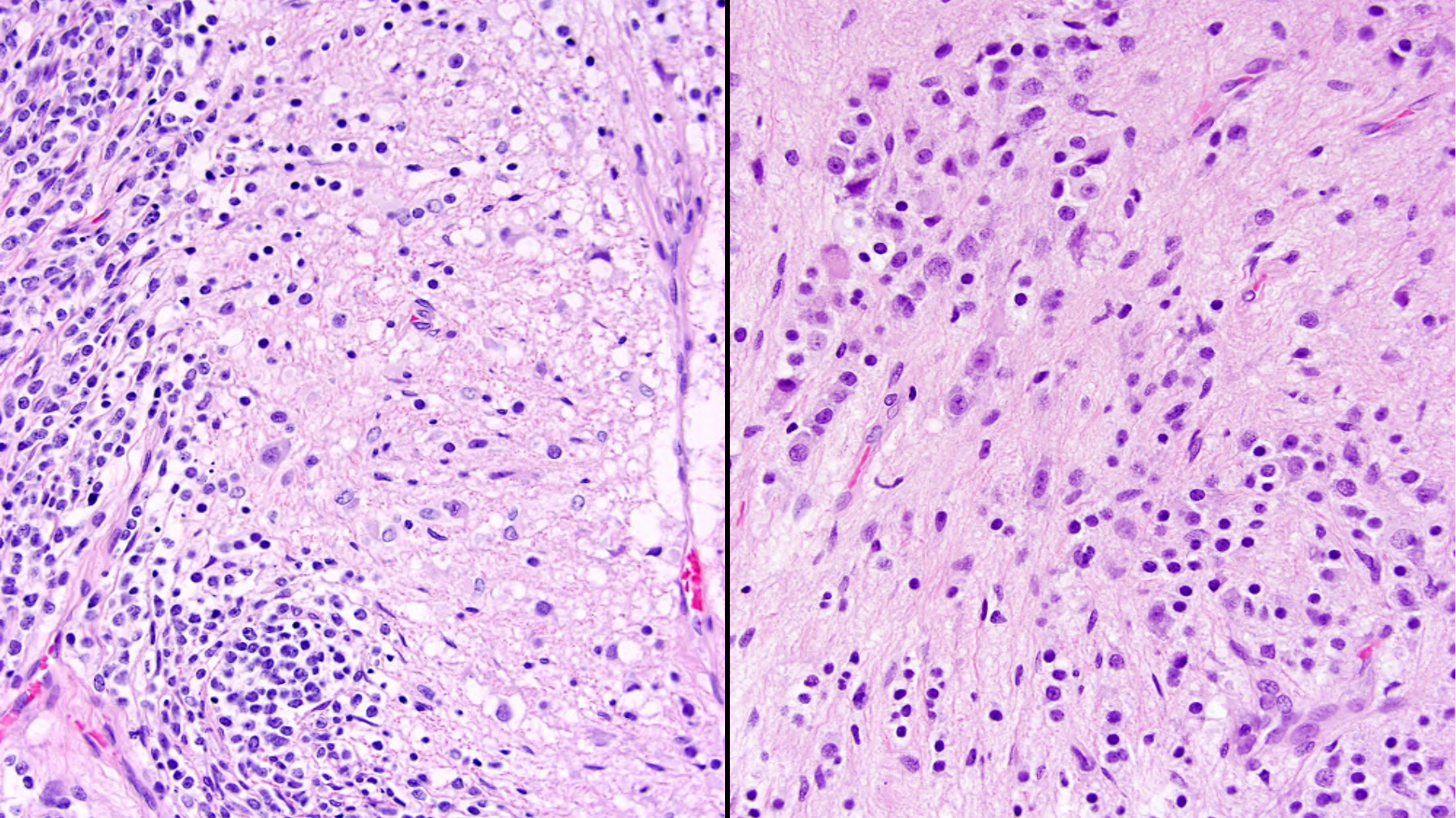
- Choroid plexus carcinoma
  - Rare tumor, but strong syndromic association
  - Infant
  - p53 IHC strong and extensive or completely negative
- Diffuse astrocytic gliomas (may have a giant cell component)
  - Young kids: IDH-wildtype HGG, often *NF1*-mutant, *NMYC*-amplified
  - Young adults: IDH-mutant astrocytomas, mostly low-grade, often *IDH1* p.R132C or p.R132S
- Medulloblastoma, SHH-activated and *TP53*-mutant
  - Most often a “middle aged kid”
  - Most often large cell/anaplastic histology

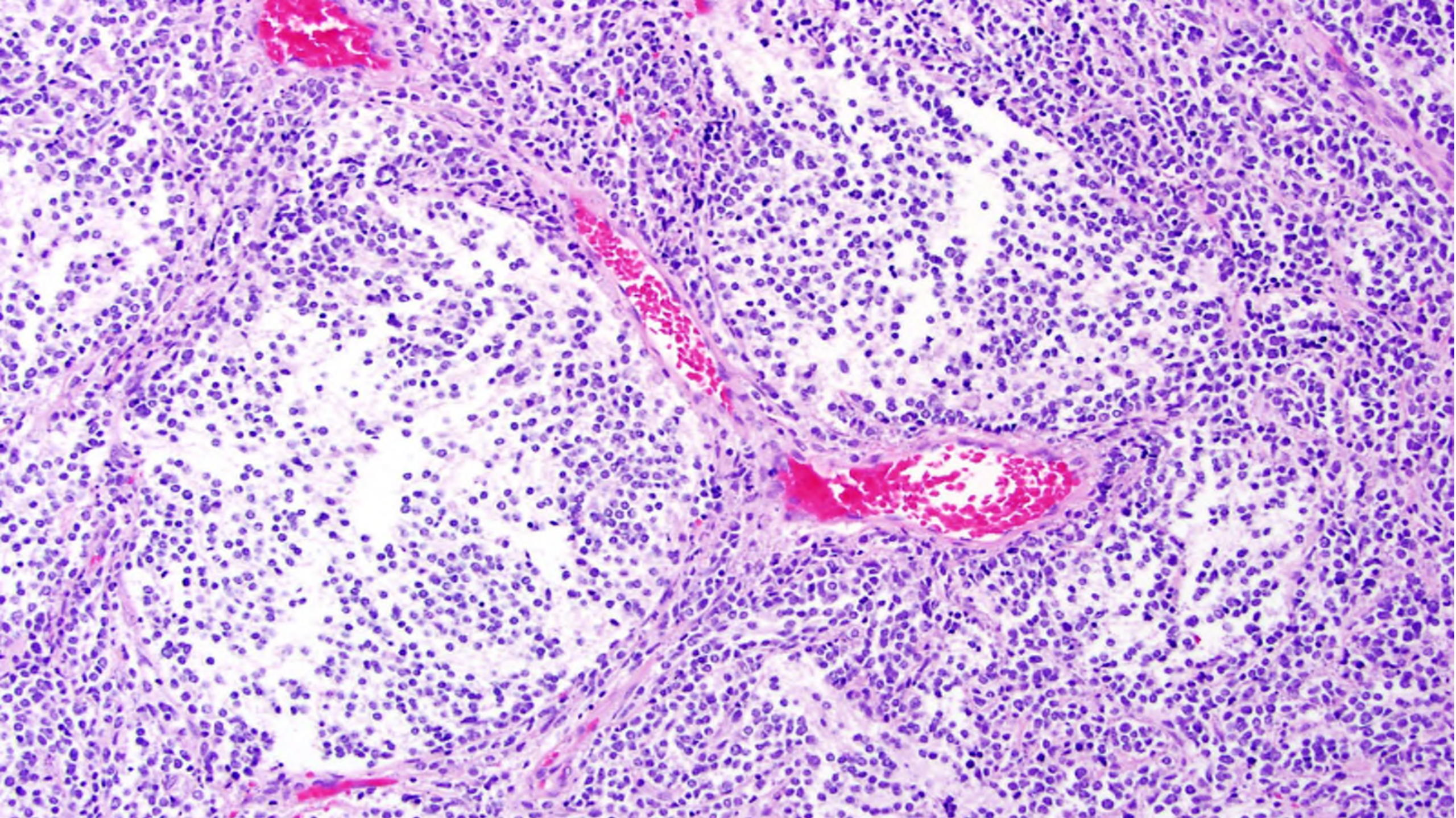
CASE 3

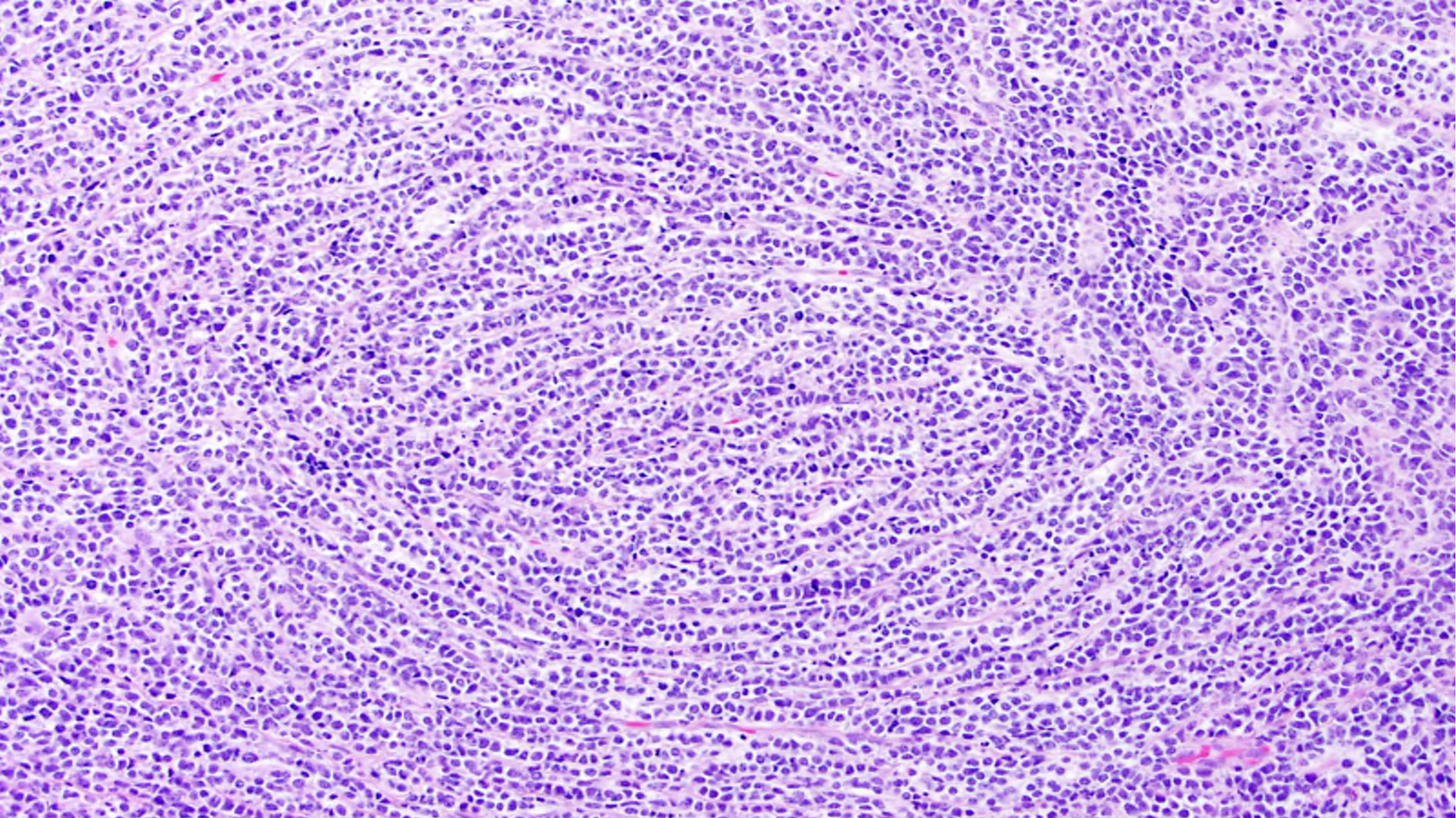
- 2-yo M with macrocephaly, developmental delay, poor balance, and 3-4 weeks of headaches
- MRI: 6.9 cm heterogeneously enhancing, midline PF mass

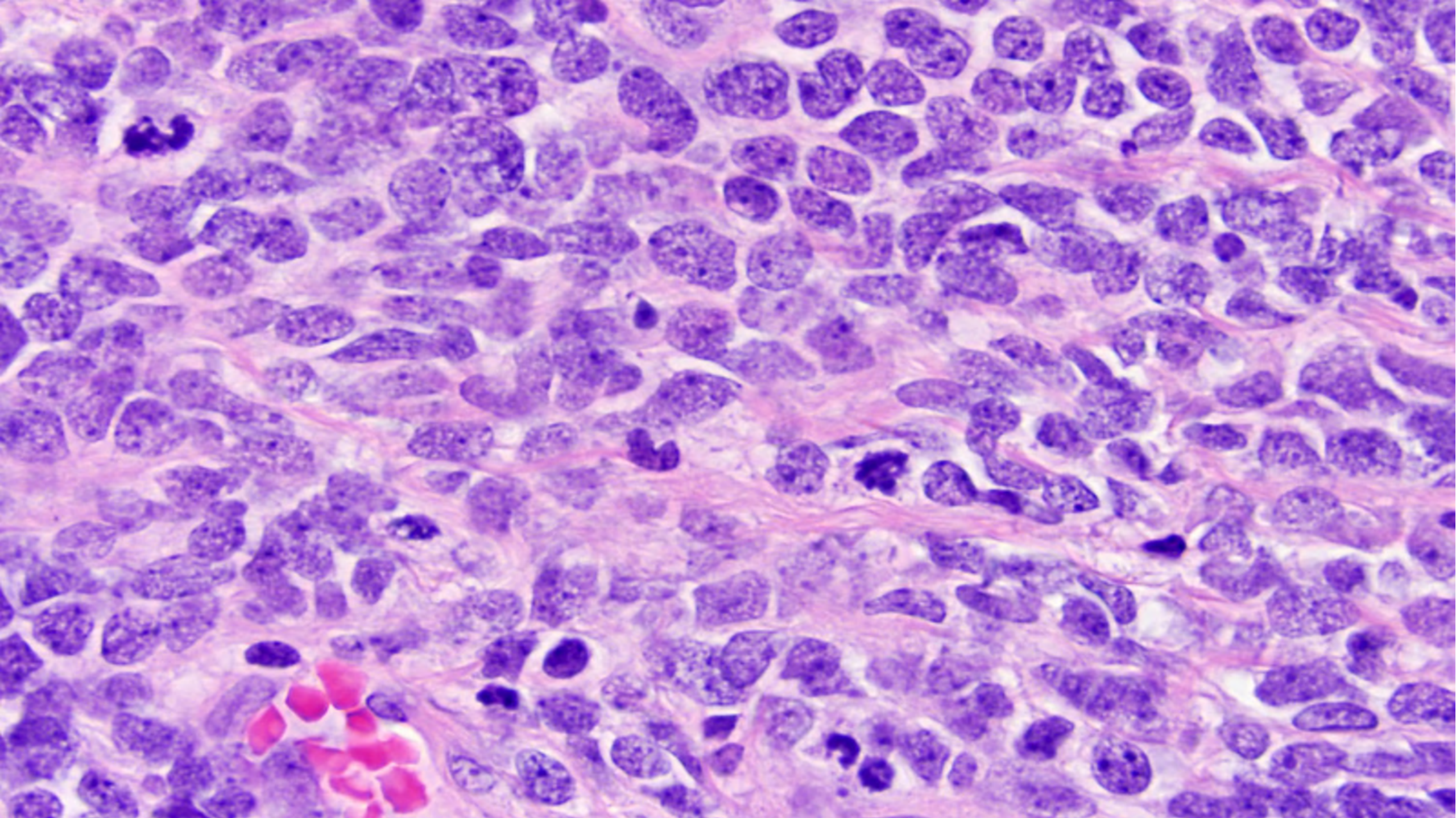


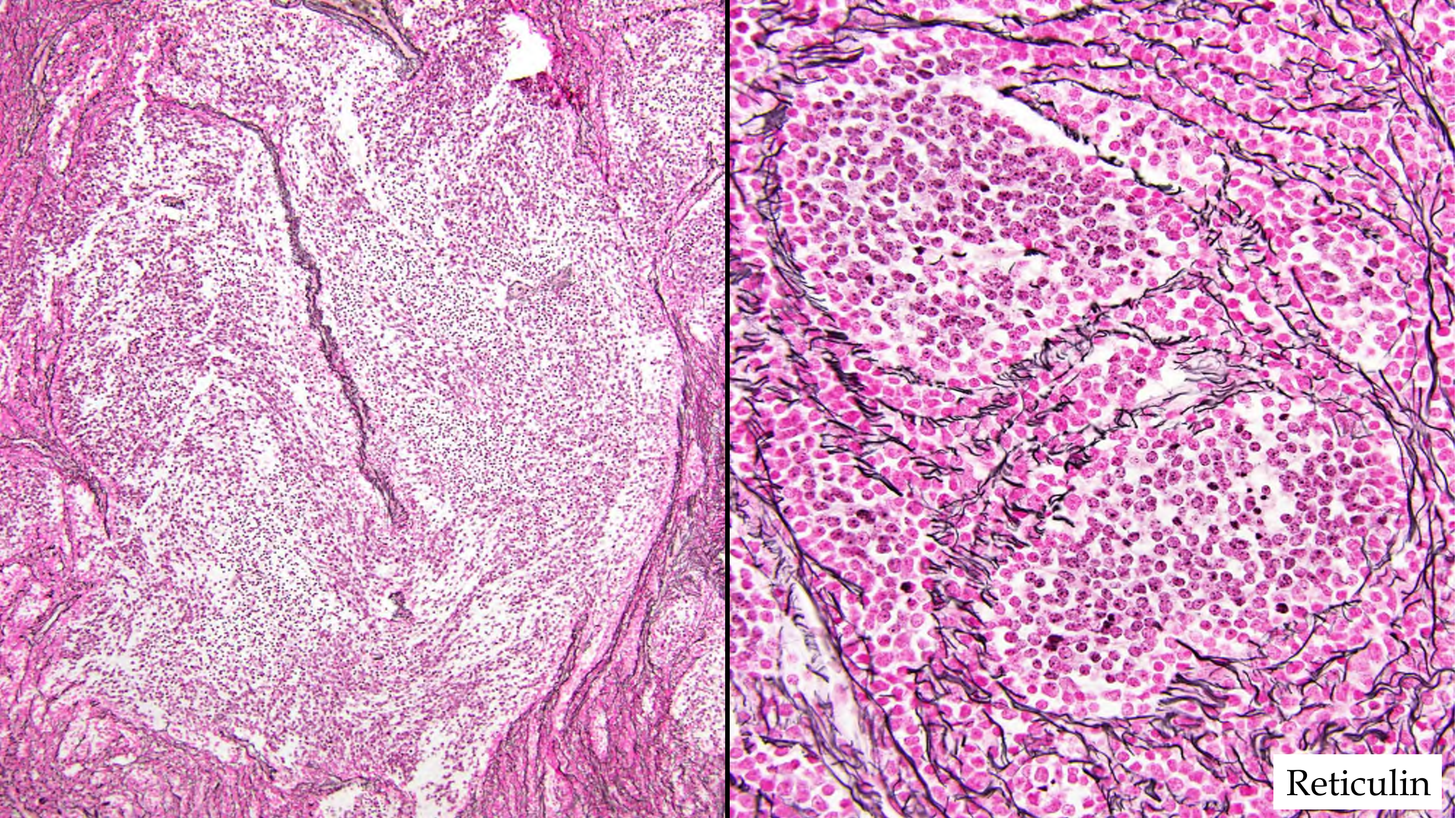


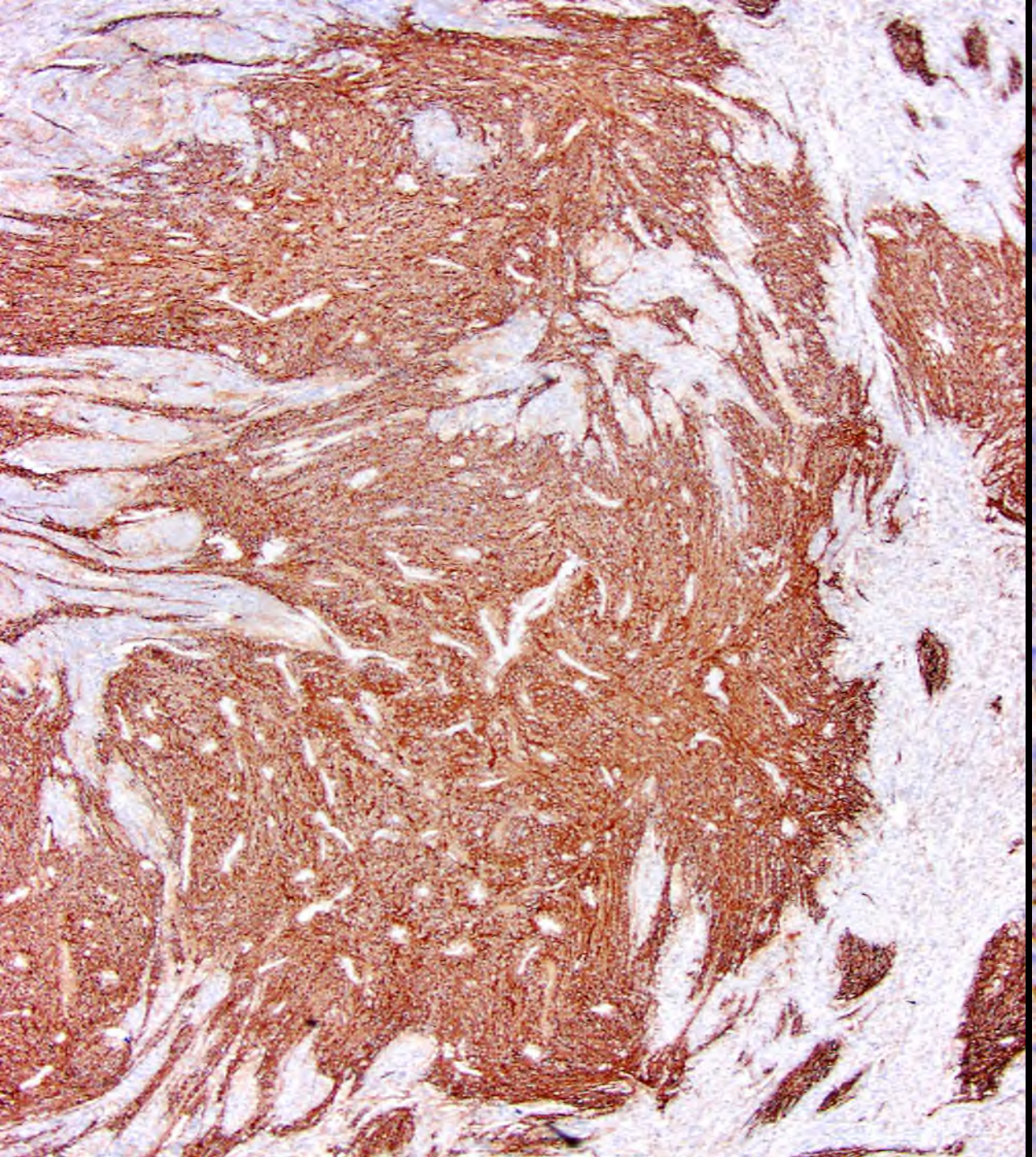


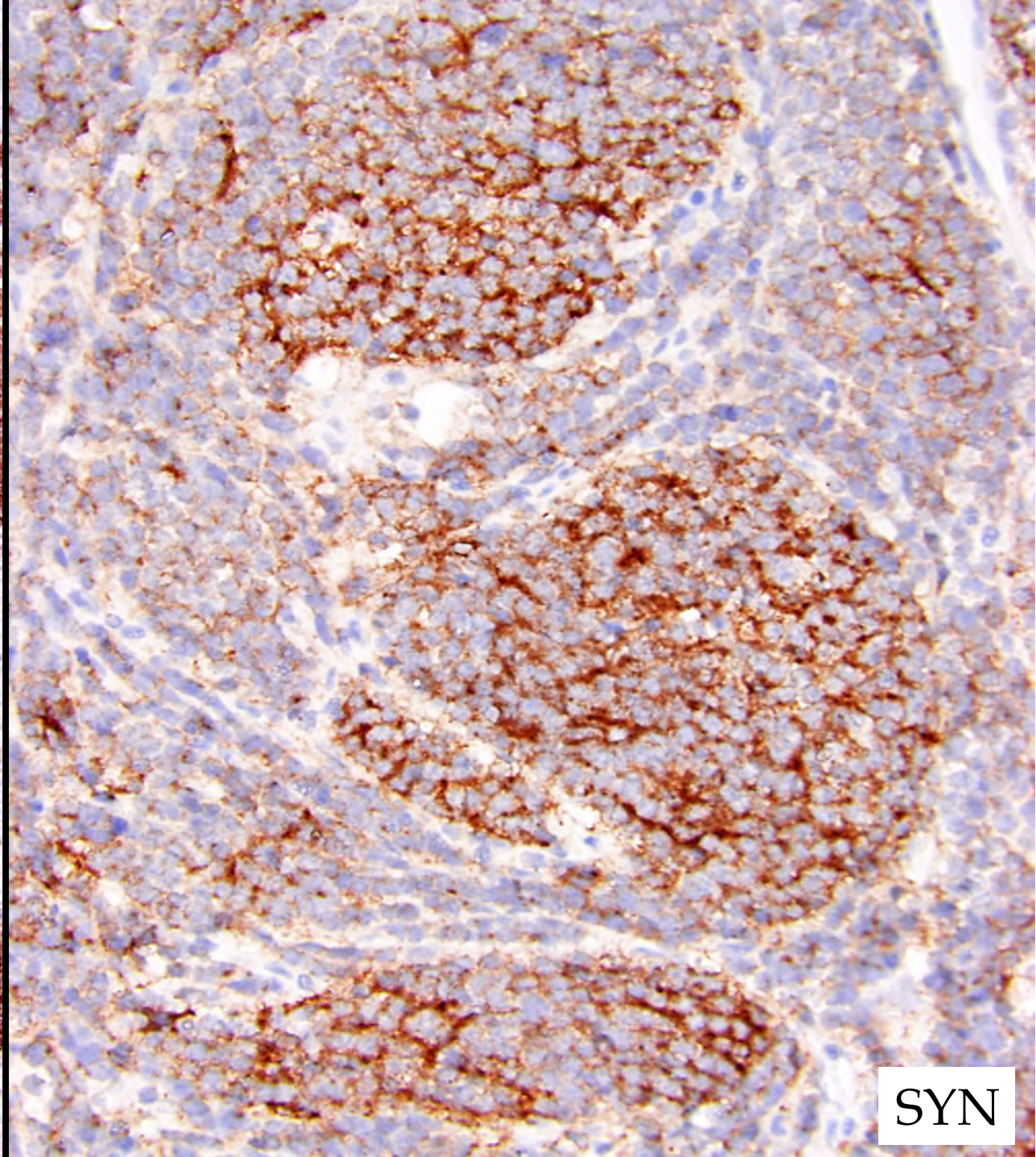


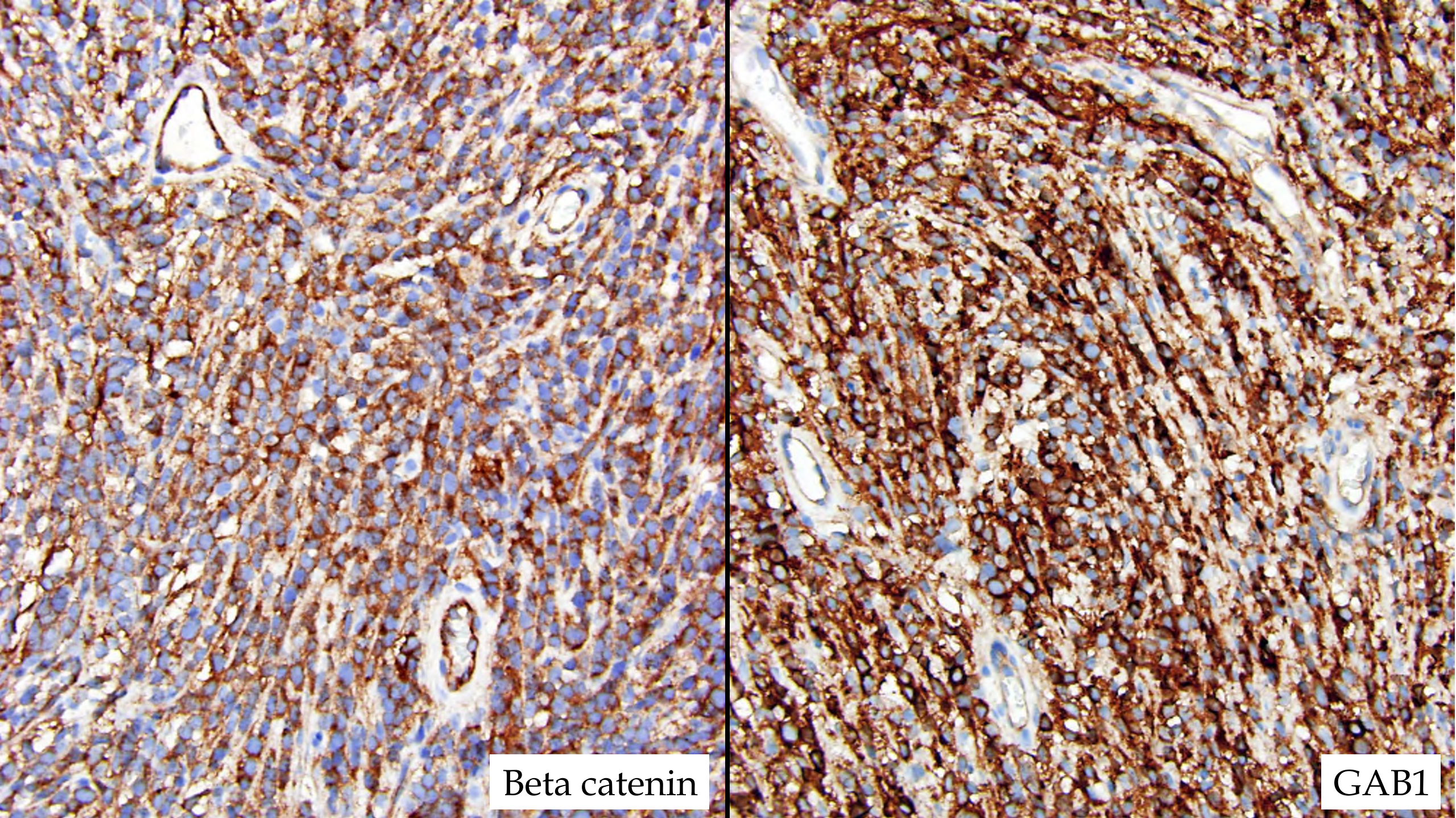





Reticulin




SYN


Beta catenin
GAB1

Initial Dx: Medulloblastoma, extensively nodular histologic type, SHH-activated and likely *TP53*-wildtype molecular group, WHO grade 4

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GENOMIC ALTERATIONS IN THE TUMOR SAMPLE				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**COVERAGE**	**MUTANT ALLELE FREQUENCY**
SUFU p.I57fs (hemizygous)	NM_016169	Pathogenic	291	99%
KDM6A p.R172* (hemizygous)	NM_021140	Pathogenic	389	95%

'Coverage' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

GENOMIC ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**COVERAGE**	**MUTANT ALLELE FREQUENCY**
SUFU p.I57fs	NM_016169	Pathogenic	212	57%

***Germline variants are only reported if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist.**

INTERPRETATION

An inactivating frameshift mutation in SUFU is present in both the normal and tumor samples, with copy neutral loss of heterozygosity in the tumor. The tumor also harbors a nonsense mutation in KDM6A (also known as UTX which is located on the X chromosome and thus has high MAF due to hemizygosity).

The copy number profile shows hemizygous losses on chromosomes 17 (including TP53) and 19, however, no focal or deep deletions are seen. No focal high level amplifications were identified including MYC, MYCN, or GLI2. No mutations were found in CTNNB1, PTCH1, SMO, TP53, or TERT promoter.

The genetic profile is consistent with an SHH pathway activated medulloblastoma due to the presence of inactivating SUFU mutation [refs. 1-2]. Of note, SUFU mutation has been correlated with those SHH pathway activated medulloblastomas which demonstrate resistance to small molecule inhibitors of SMO [ref. 3]. Mutations in the histone demethylase gene KDM6A have been previously reported in a subset of medulloblastomas [refs. 4].

The presence of germline SUFU mutation is causative of a Gorlin-like syndrome which is known to increase incidence of medulloblastoma as well as meningioma and basal cell carcinoma [refs. 5-7]. Genetic counseling is

Final Dx: Medulloblastoma, extensively nodular histologic type, SHH-activated and *TP53*-wildtype molecular group, WHO grade 4, arising in setting of nevoid basal cell carcinoma (Gorlin) syndrome

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ORIGINAL REPORT

High Frequency of Germline *SUFU* Mutations in Children With Desmoplastic/Nodular Medulloblastoma Younger Than 3 Years of Age

Laurence Brugières, Audrey Remenieras, Gaëlle Pierron, Pascale Varlet, Sébastien Forget, Véronique Byrde, Johny Bombled, Stéphanie Puget, Olivier Caron, Christelle Dufour, Olivier Delattre, Brigitte Bressac-de Paillerets, and Jacques Grill

See accompanying article on page 2154

Laurence Brugières, Audrey Remenieras, Sébastien Forget, Véronique Byrde, Johny Bombled, Olivier Caron, Christelle Dufour, Brigitte Bressac-de Paillerets, and Jacques Grill, Institut Gustave Roussy, Villejuif; Gaëlle Pierron and Olivier Delattre, Institut Curie, Centre Hospitalier; Olivier Delattre, Institut National de la Santé et de la Recherche Médicale (INSERM) U830; Pascale Varlet, Sainte-Anne Hospital, INSERM U894; Stéphanie Puget, Hôpital Necker Enfants Malades; and Brigitte Bressac-de Paillerets, Unité INSERM U946/Fondation Jean Dausset–Centré d'Étude du Polymorphisme Humain, Paris, France.

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Supported by the Centre de Recherche sur les tumeurs de l'Enfant, Villejuif, and the Association "L'Etoile de Martin," Paris, France.

Presented in part in poster format at the 60th Annual Meeting of the American Society of Human Genetics, November 2-6, 2010, Washington, DC.

ABSTRACT

Purpose

Germline mutations of the *SUFU* gene have been shown to be associated with genetic predisposition to medulloblastoma, mainly in families with multiple cases of medulloblastoma and/or in patients with symptoms similar to those of Gorlin syndrome. To evaluate the contribution of these mutations to the genesis of sporadic medulloblastomas, we screened a series of unselected patients with medulloblastoma for germline *SUFU* mutations.

Patients and Methods

A complete mutational analysis of the *SUFU* gene was performed on genomic DNA in all 131 consecutive patients treated for medulloblastoma in the pediatrics department of the Institut Gustave Roussy between 1972 and 2009 and for whom a blood sample was available.

Results

We identified eight germline mutations of the *SUFU* gene: one large genomic duplication and seven point mutations. Mutations were identified in three of three individuals with medulloblastoma with extensive nodularity, four of 20 with desmoplastic/nodular medulloblastomas, and one of 108 with other subtypes. All eight patients were younger than 3 years of age at diagnosis. The mutations were inherited from the healthy father in four of six patient cases in which the parents accepted genetic testing; de novo mutations accounted for the other two patient cases. Associated events were macrocrania in six patients, hypertelorism in three patients, and multiple basal cell carcinomas in the radiation field after age 18 years in one patient.

Conclusion

These data indicate that germline *SUFU* mutations were responsible for a high proportion of desmoplastic medulloblastoma in children younger than 3 years of age. Genetic testing should be offered to all children diagnosed with sonic hedgehog–driven medulloblastoma at a young age.

NBCCS (Gorlin syndrome)

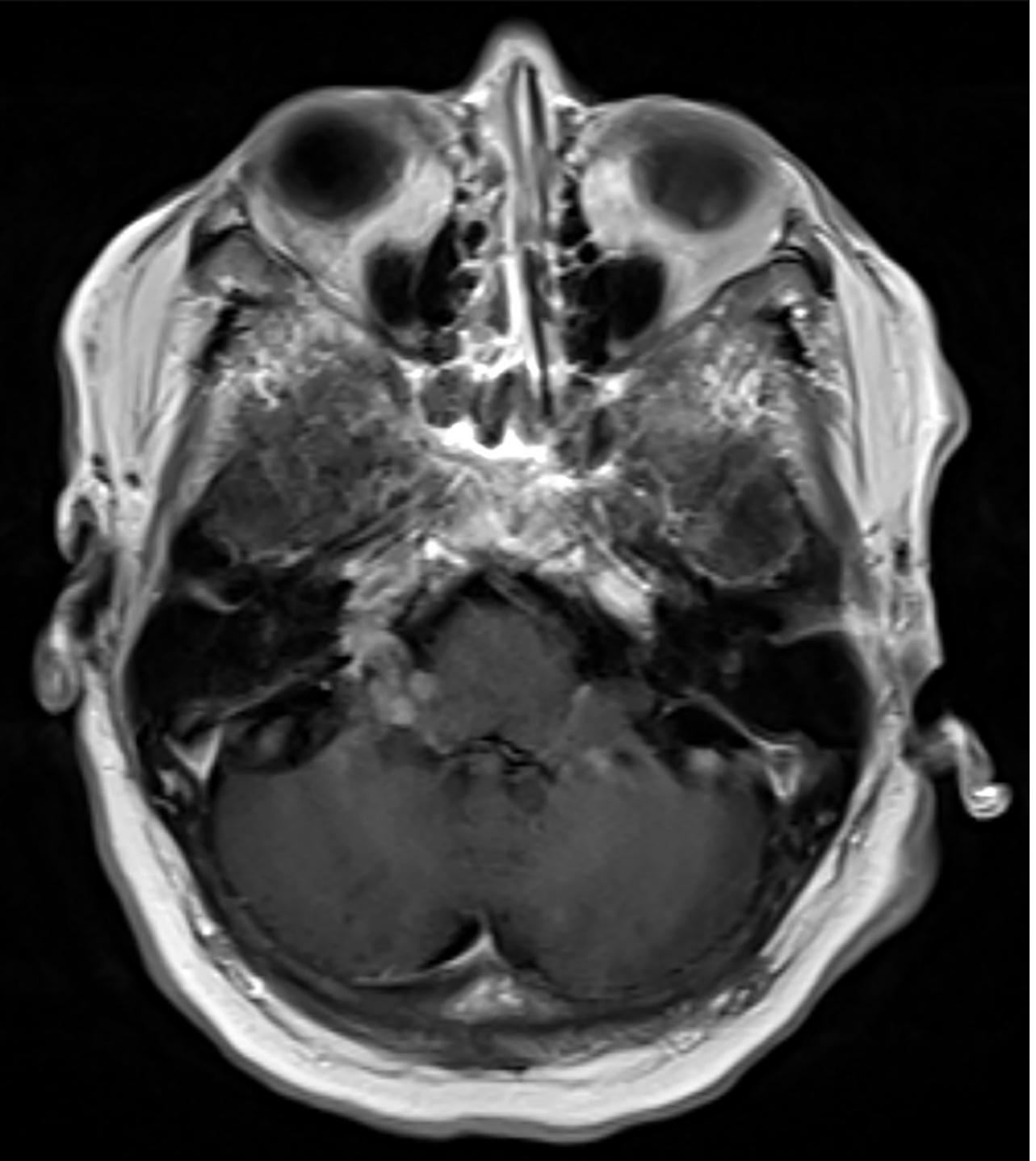
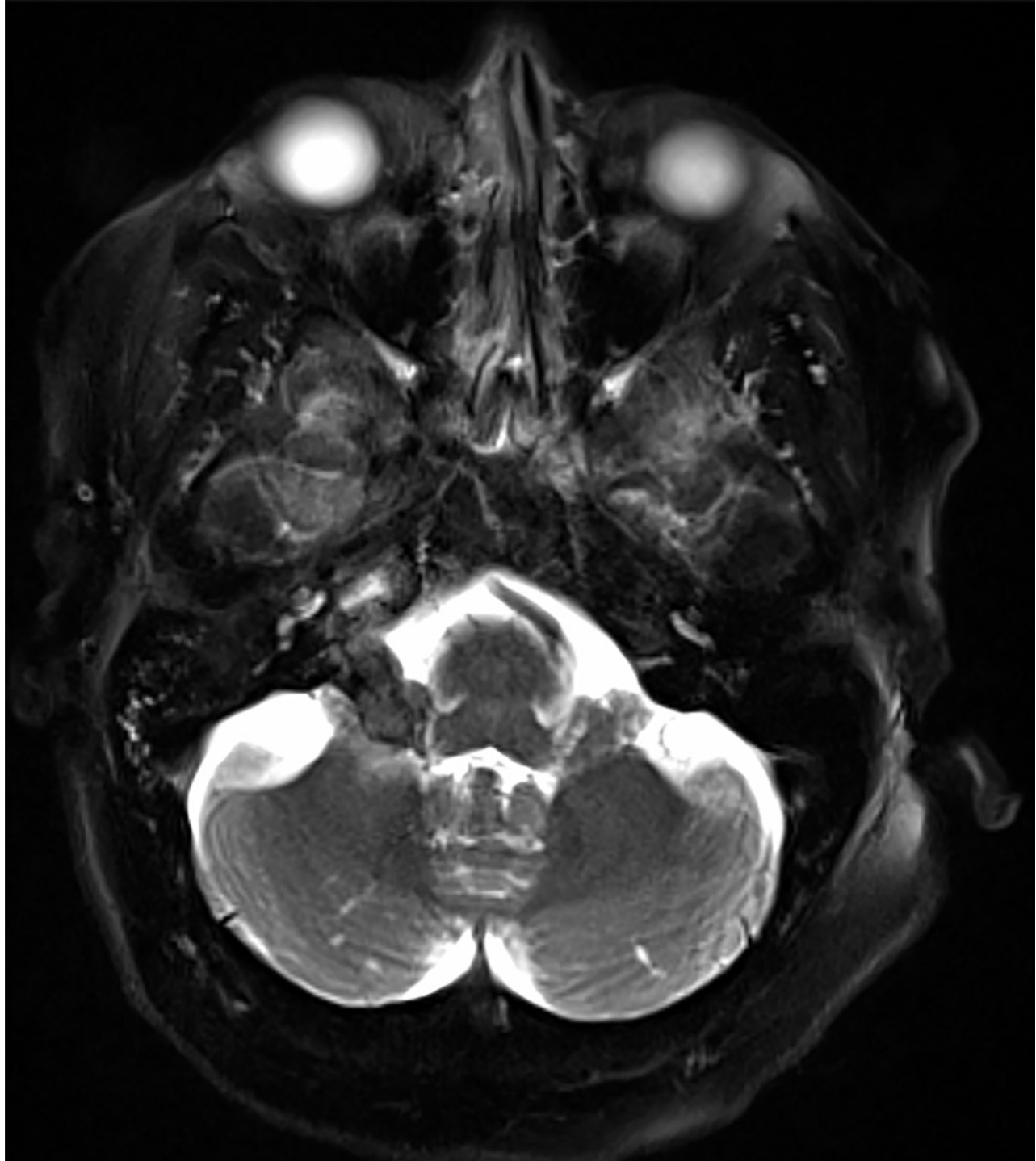
- Germline *PTCH1* variants more common than *SUFU*, but the latter associated with much higher risk of medulloblastoma
- Typically, D/N or EN medulloblastoma histology
- SHH-activated and *TP53*-wildtype molecular group
- Radiation therapy withheld if possible since high risk of BCC and other secondary tumors (e.g., meningioma)
- Malformations in *PTCH1* variants; less clear with *SUFU*

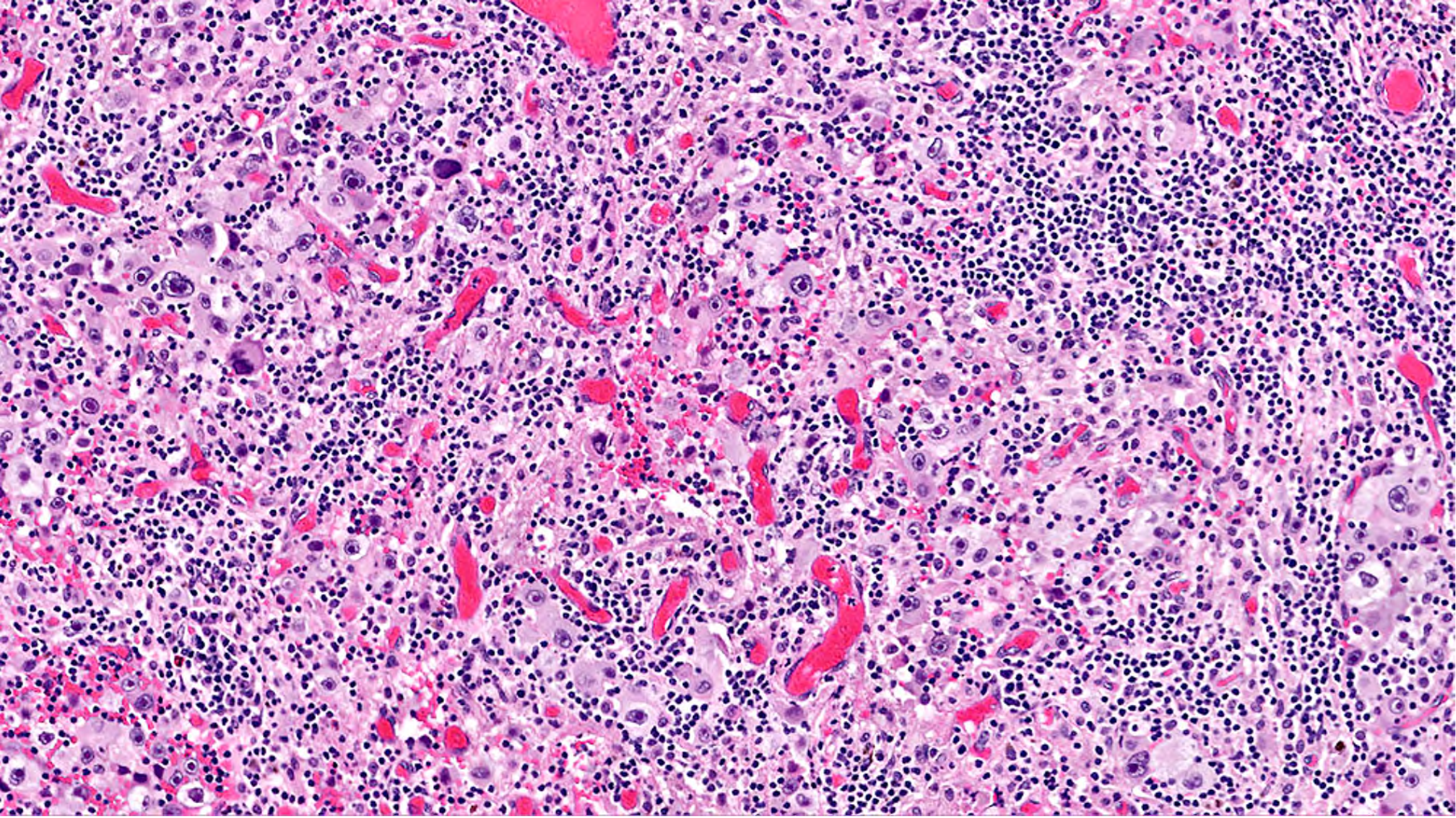
Rhabdoid tumor predisposition syndrome (RTPS)

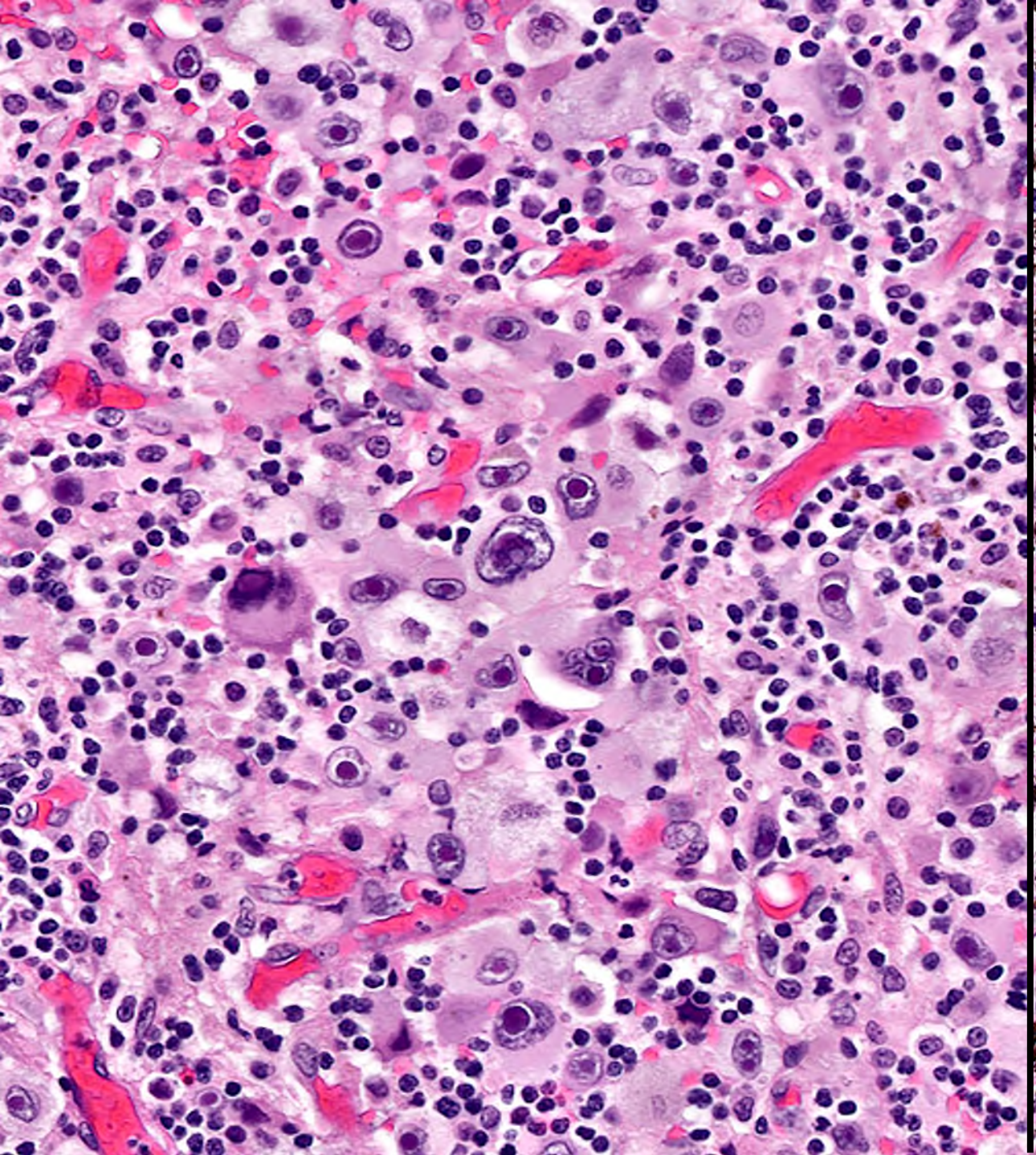
- 25–35% of all AT/RT arise in setting of RTPS
- Most patients under 1 year of age
- Predisposed to multiple MRTs and AT/RTs
- Germline variants of either *SMARCB1* (RTPS1) or *SMARCA4* (RTPS2-exceedingly rare)
- IHC surrogates include INI1 (RTPS1) and BRG1 (RTPS2), but tumor staining doesn’t distinguish familial from sporadic AT/RT

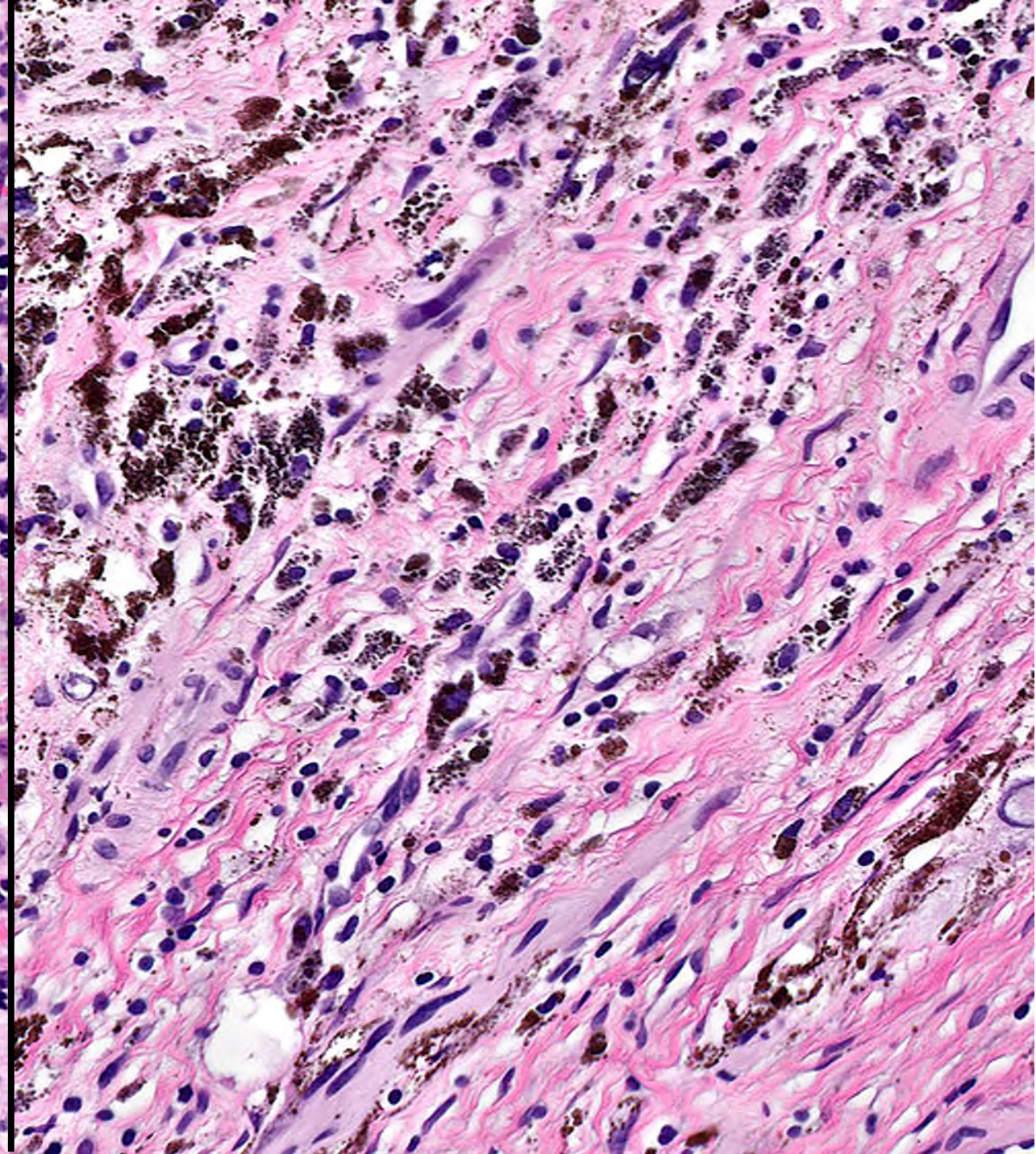
CASE 4

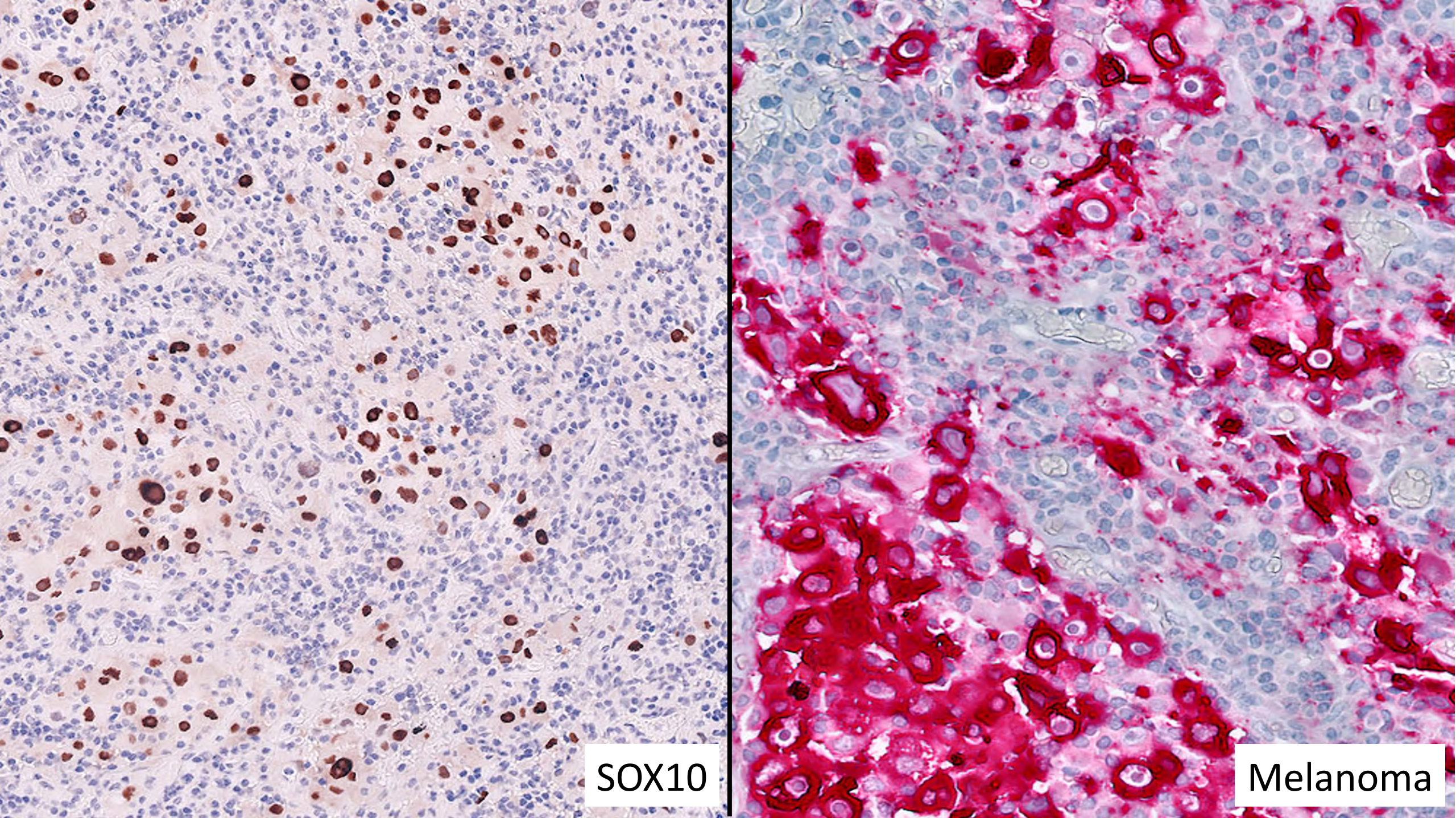
- 60-yo F with right sided hearing loss
- MRI: 2.3 cm enhancing mass in R prepontine cistern extending to the jugular bulb

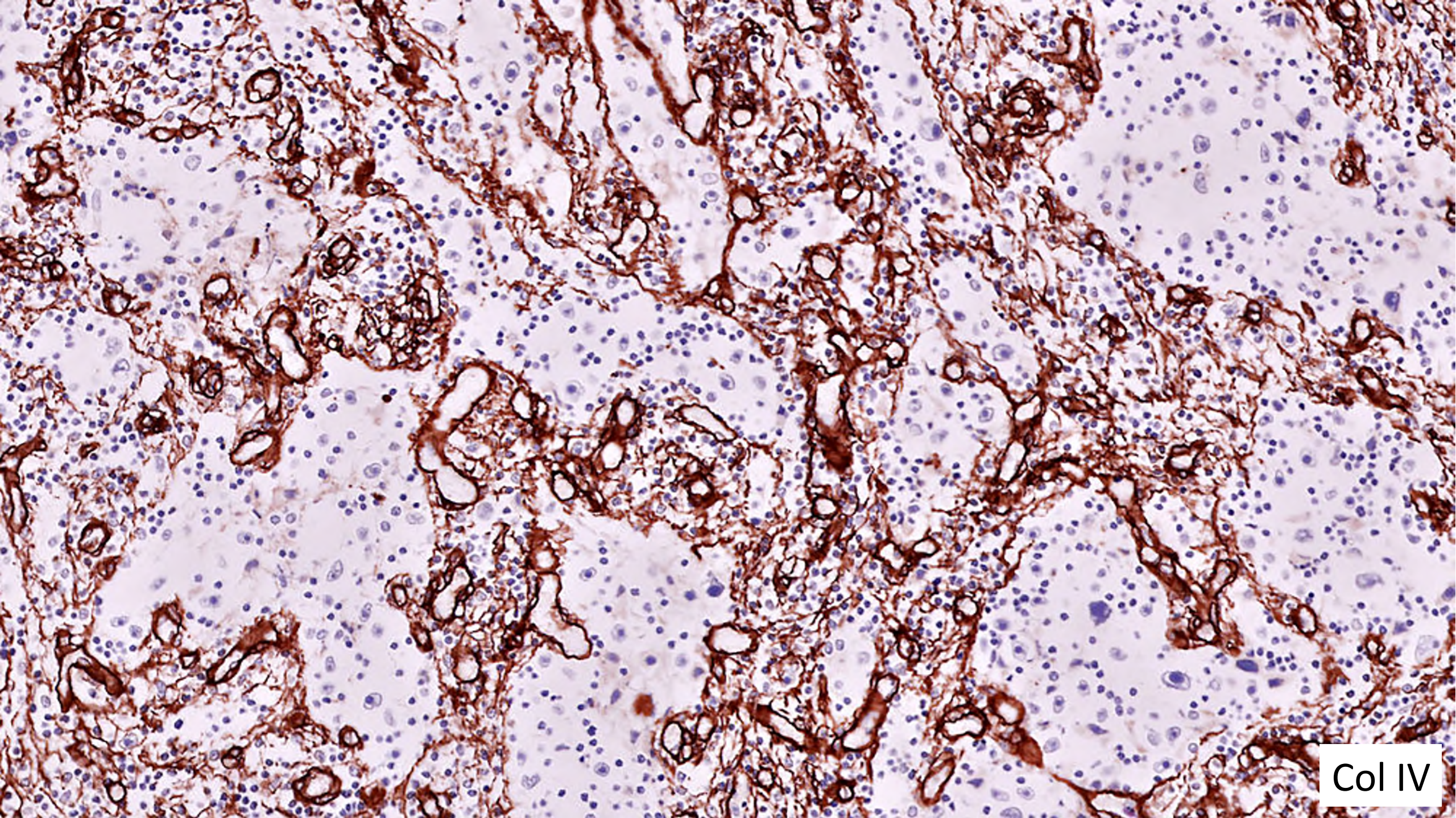



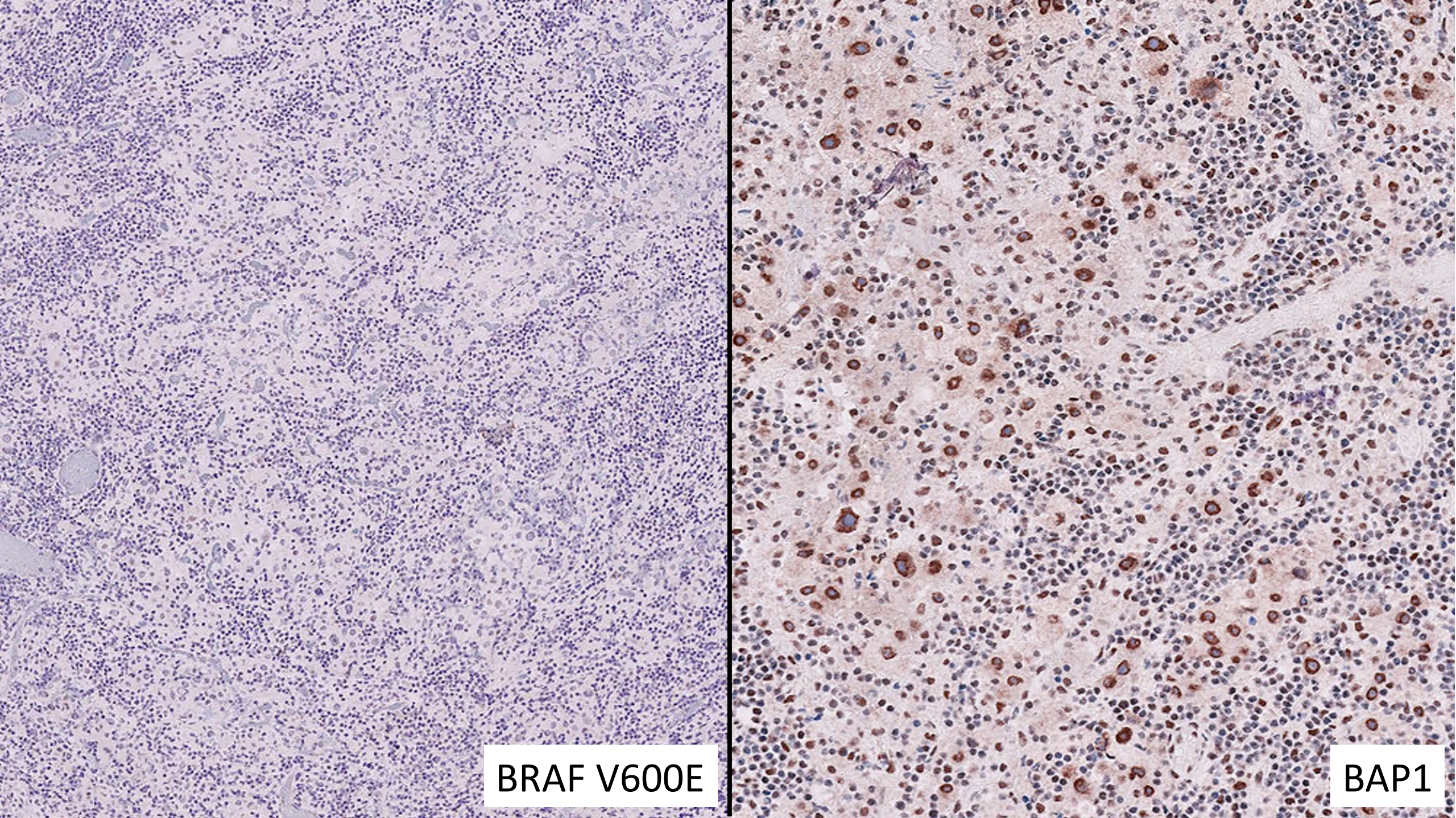


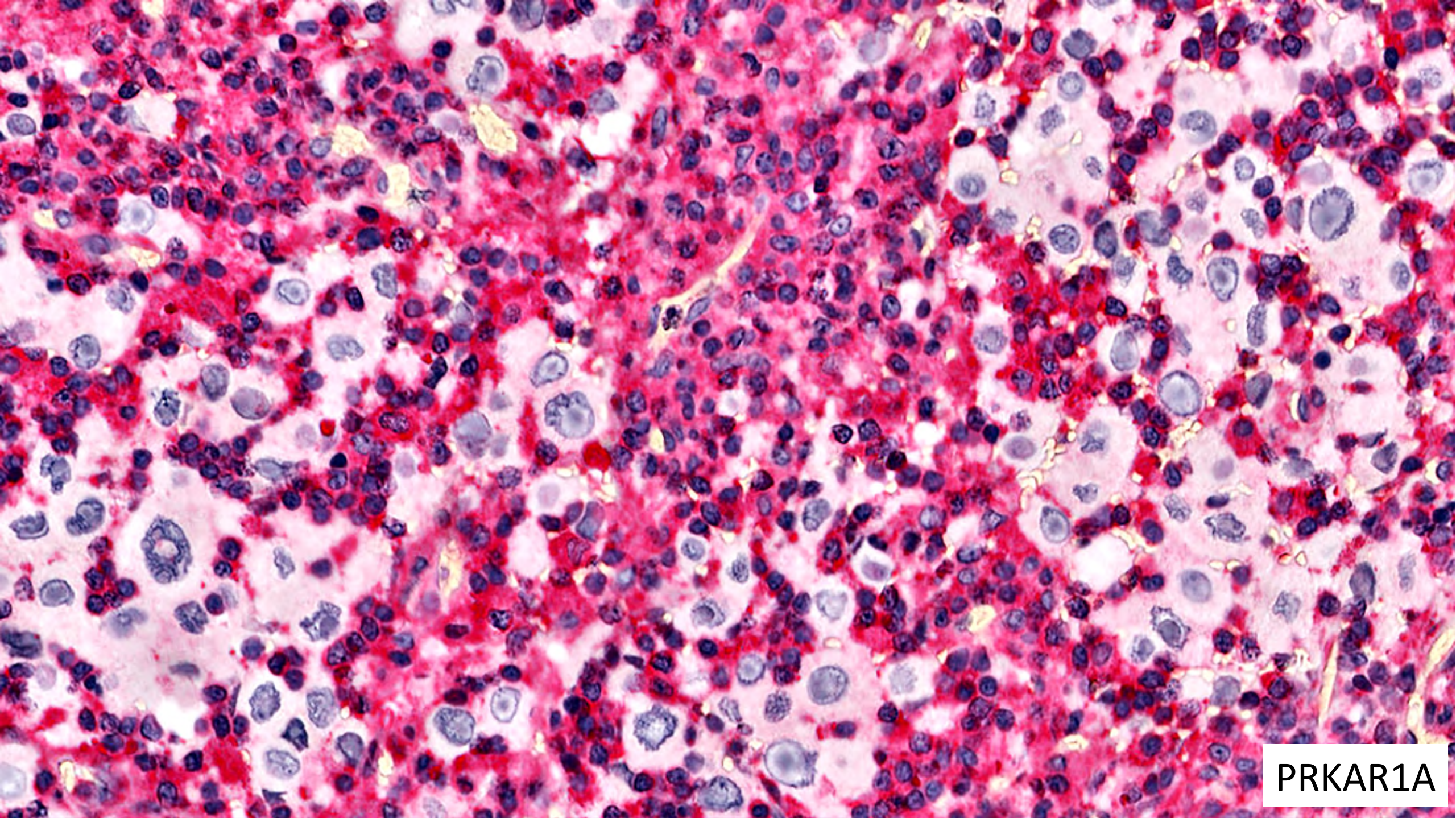





SOX10
Melanoma


Col IV


BRAF V600E
BAP1

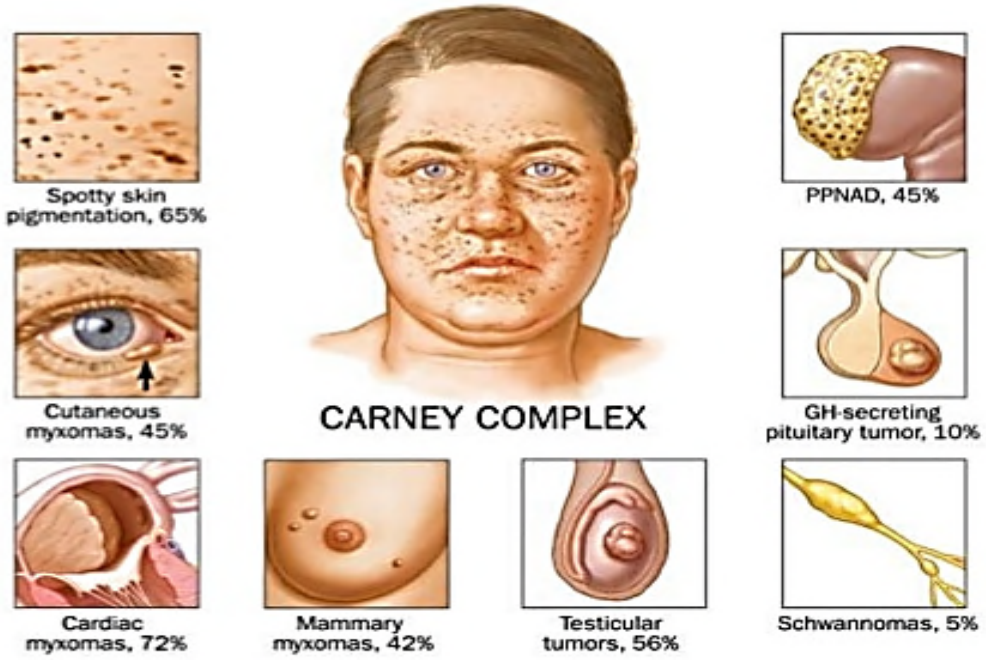

PRKAR1A

Review of Medical Records: Prior history of cardiac myxoma

Final Dx: Malignant melanotic nerve sheath tumor (MMNST), arising in the setting of Carney Complex

Carney Complex

- CNC1 due to germline *PRKAR1A* variant (~70%)
- CNC2: uncertain genetics; usually milder disease



Characteristics of carney complex. (n.d.). Retrieved from http://www.mayoclinic.org/medicalprofs/enlargeimage5833.html

Carney Complex

Major diagnostic criteria:

Spotty skin pigmentation with typical distribution (lips, conjunctiva, inner or outer canthi, vaginal or penile mucosa)

Cardiac myxoma[a]

Myxoma (cutaneous and mucosal)[a]

Breast myxomatosis[a] or fat-suppressed MRI findings suggestive of this diagnosis

Primary pigmented nodular adrenocortical disease[a] or paradoxical positive response of urinary glucocorticoid excretion to dexamethasone administration during the Liddle test

Acromegaly due to growth hormone (GH)-producing pituitary adenoma / pituitary neuroendocrine tumour (PitNET)[a]

Large cell calcifying Sertoli cell tumour[a] or characteristic calcification on testicular ultrasound

Thyroid follicular adenoma or carcinoma[a] or multiple, hypoechoic nodules on thyroid ultrasound in a young patient

Malignant melanotic nerve sheath tumour[a]

Blue naevus, epithelioid blue naevus (multiple)[a]

Breast ductal adenoma (multiple)[a]

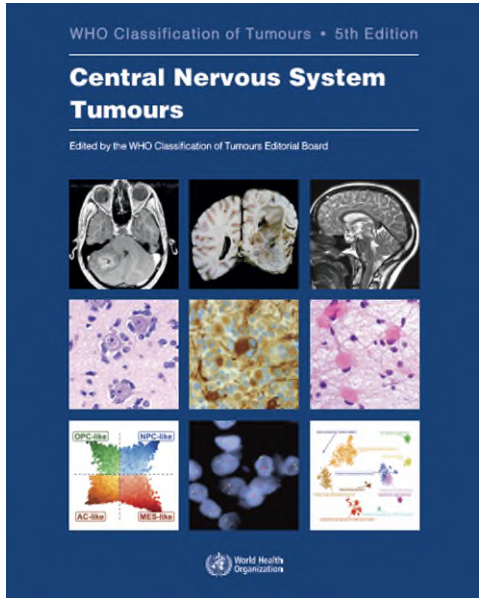
Osteochondromyxoma[a]

Supplemental criteria:

Affected first-degree relative

Inactivating mutation of the *PRKAR1A* gene

[a]These tumours all require histological confirmation.



Malignant Melanotic Schwannian Tumor

A Clinicopathologic, Immunohistochemical, and Gene Expression Profiling Study of 40 Cases, With a Proposal for the Reclassification of "Melanotic Schwannoma"

Jorge Torres-Mora, MD, Sarah Dry, MD,† Xinmin Li, PhD,† Scott Binder, MD,† Mitual Amin, MD,‡ and Andrew L. Folpe, MD**

Abstract: Melanotic schwannomas (MSs), variably associated with the Carney complex, are rare tumors that usually involve spinal nerve roots but may occur in other locations. Clinicopathologic evaluation poorly predicts the behavior of MS. Fewer than 200 cases have been reported. We report a series of 40 well-characterized MSs, one of the largest series to date. The tumors were comprehensively evaluated, and clinical follow-up was obtained. Immunohistochemistry for S100 protein, Melan-A, HMB45, tyrosinase, glial fibrillary acidic protein (GFAP), EMA, SMARCB1, Ki-67 antigen, ASMTL, and the Carney complex–associated PRKAR1A gene product was performed using commercially available antibodies and the Ventana Ultraview detection system. Gene microarray study was conducted on formalin-fixed, paraffin-embedded blocks from 10 MSs and the results compared with previous data from melanoma and schwannoma. Differentially expressed genes were selected at >3-fold and $P < 0.001$. The Fisher exact test was used for statistical analysis. The tumors occurred in 18 male and 22 female patients (mean age 41 y; range, 11 to 84 y) and involved the paravertebral nerve roots (N = 31), mediastinum (N = 3), sacrum, cauda equina, para-aortic region, fifth cranial nerve, buttock, and cerebellum (N = 1 each). Two patients had known Carney complex, and 1 patient also had a cutaneous myxoma, suggestive of Carney complex. The tumors expressed S100 protein (21/25, 84%), Melan-A (23/25, 92%), HMB45 (25/25, 100%), tyrosinase (25/25, 100%), GFAP (0/24, 0%), EMA (0/9, 0%), SMARCB1 (retained in 25/25, 100%), and ASMTL (5/19, 26%); PRKAR1A expression was lost in 7/20 cases (35%). Ki-67-labeling index was $<5\%$ in 23/25 cases (92%) and 5% to 10% in 2/25 cases (8%). Gene expression profiling showed significant differences between MS, melanoma, and conventional schwannoma. Clinical follow-up (26/40, 65%; mean 55 mo; range, 1 to 300 mo) showed local recurrences in 9/26 (35%) and metastases in 11/26 (44%) patients. Fourteen patients were alive without disease, 5 were alive with disease, and 7 had died of disease. Only a mitotic rate $>2/10$ HPF correlated with metastases ($P = 0.008$). The clinicopathologic features of tumors with and without psammoma bodies were identical. We conclude that MSs are distinctive malignant tumors, rather than benign neoplasms with occasionally unpredictable behavior, and propose their reclassification as "malignant melanotic schwannian tumors." Loss of PRKAR1A expression suggests a link to Carney complex, even when this history is absent.

Key Words: melanotic schwannoma, psammomatous melanotic schwannoma, sarcoma, gene expression profiling, immunohistochemistry, Carney complex, PRKAR1A

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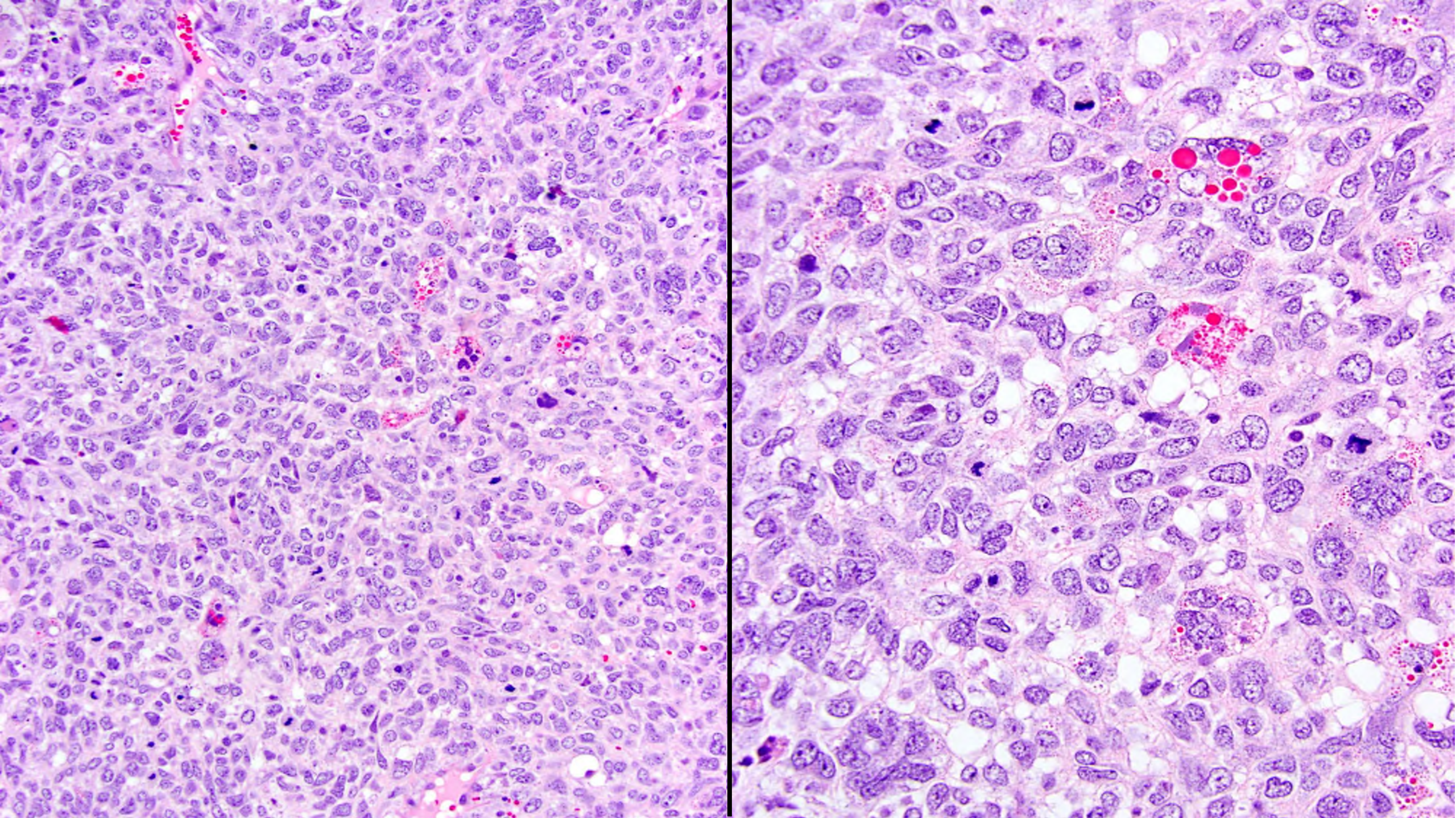
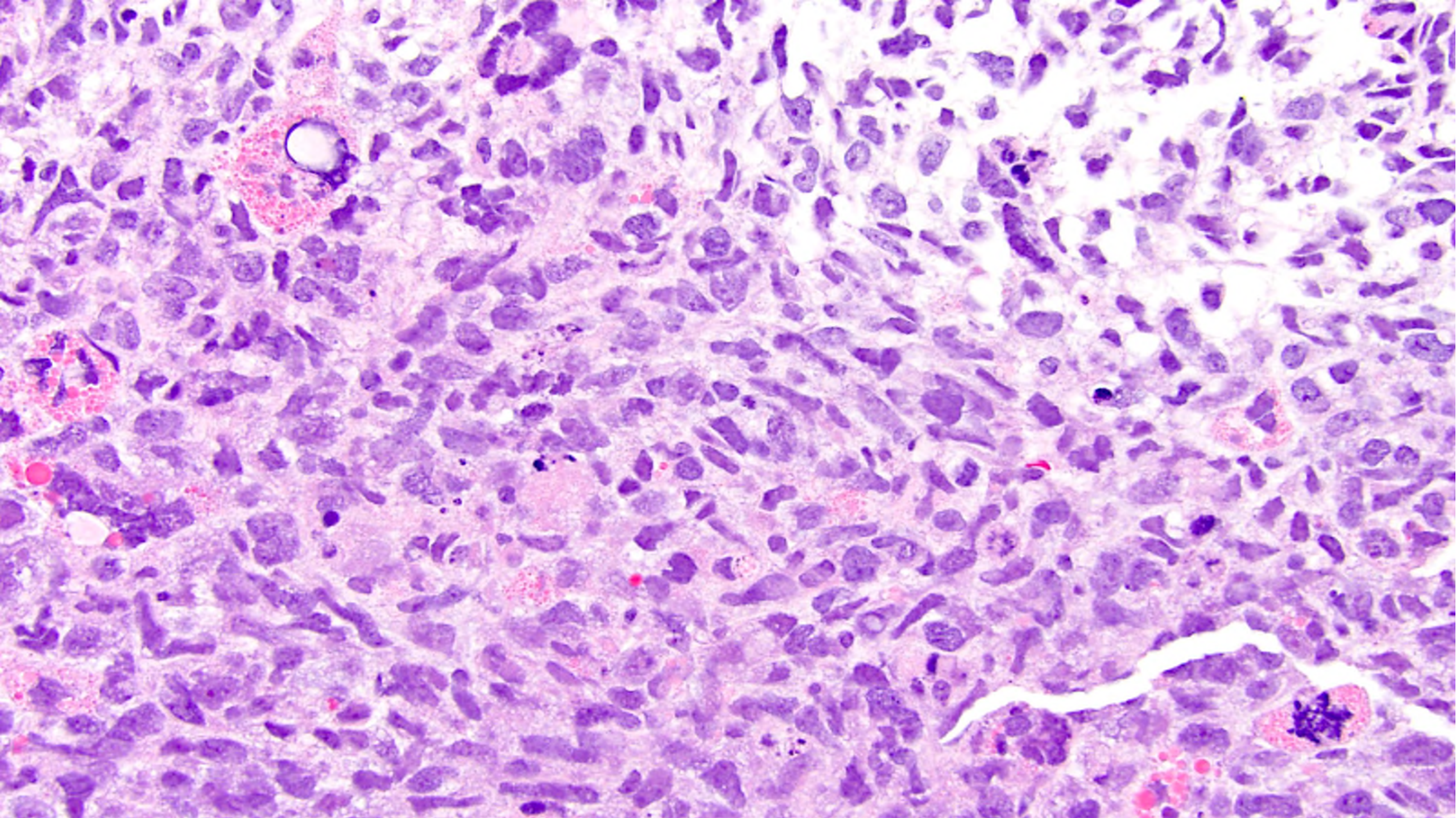
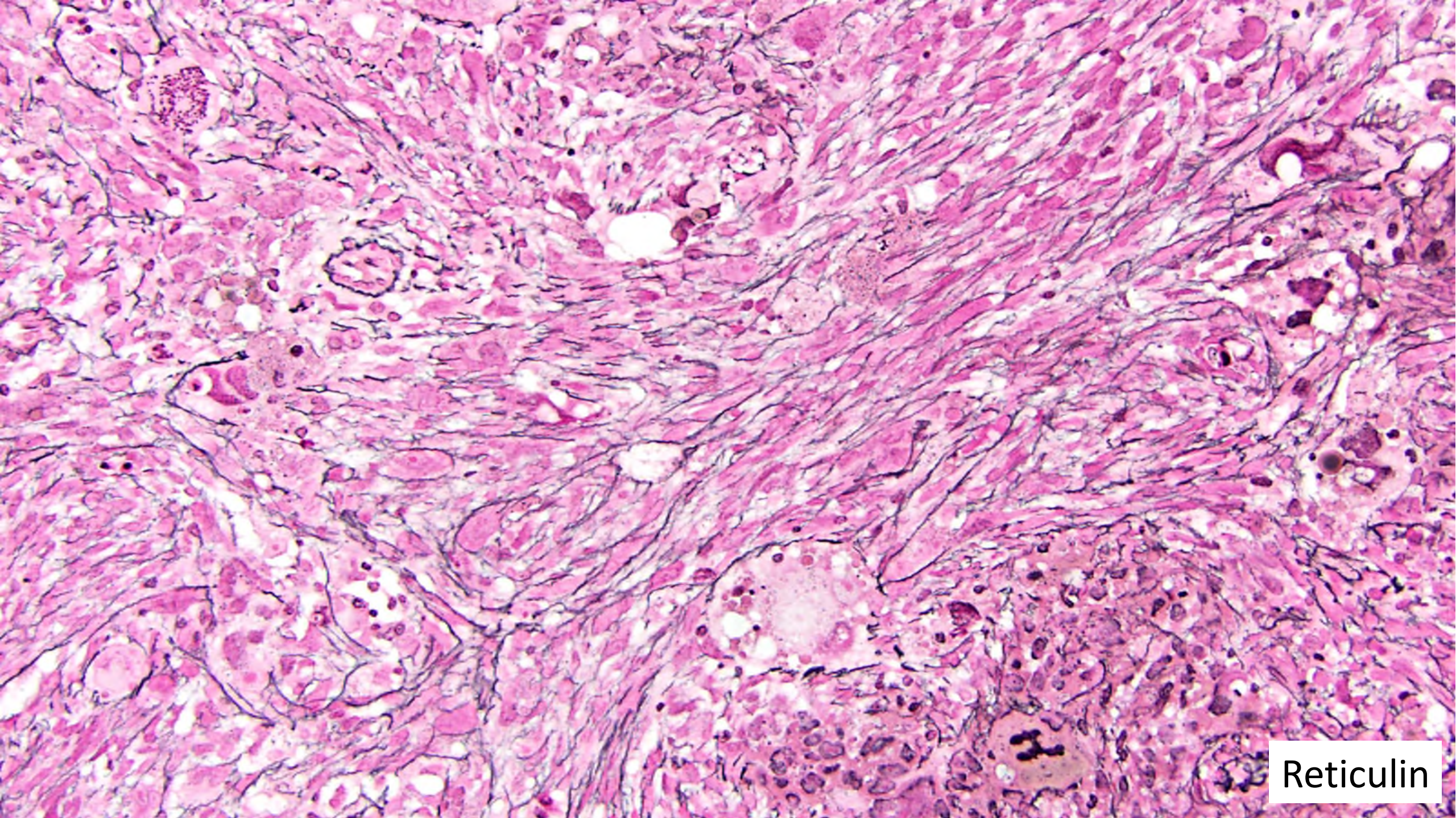
Melanotic schwannoma (MS) is a rare tumor of putative neural crest origin that was first identified in 1932 by Millar,[1] who used the descriptive term "malignant melanotic tumor of the ganglion cells arising from the thoracic sympathetic ganglion." Since then, <200 cases, most often occurring in the paraspinal nerve roots and gastrointestinal tract, have been described, chiefly in the form of case reports or small series.[2–6] In 1990, Carney[7] noted the very frequent ($\sim 50\%$) association of MS with other stigmata of Carney complex (skin pigmentary abnormalities, myxomas, endocrine tumors, or endocrine overactivity). Other studies of MS have, however, suggested a much lower association with Carney complex, ranging from 0% to 5% in 3 subsequently published series.[8–10] Although the "cell of origin" of MS

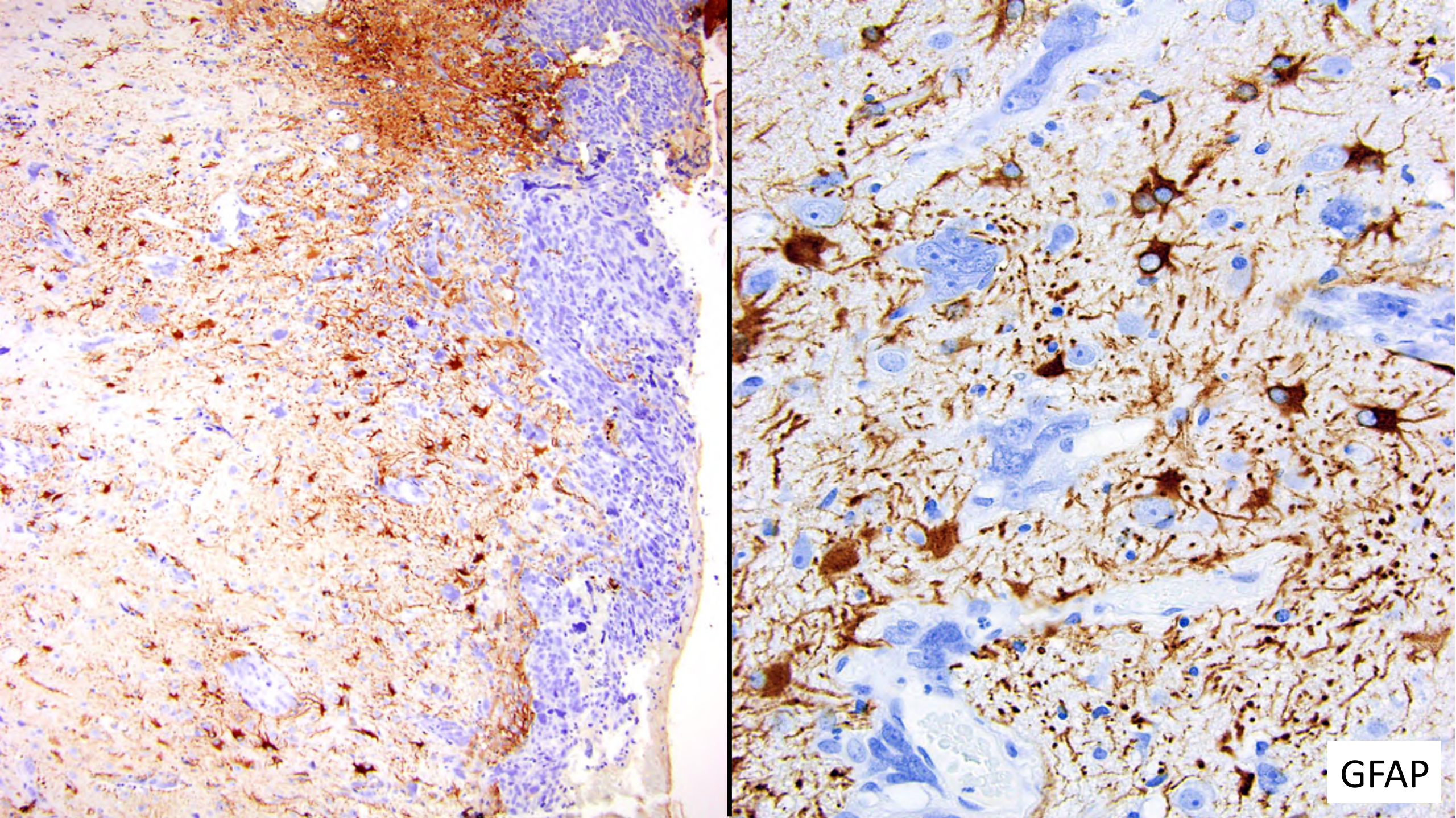
CASE 5

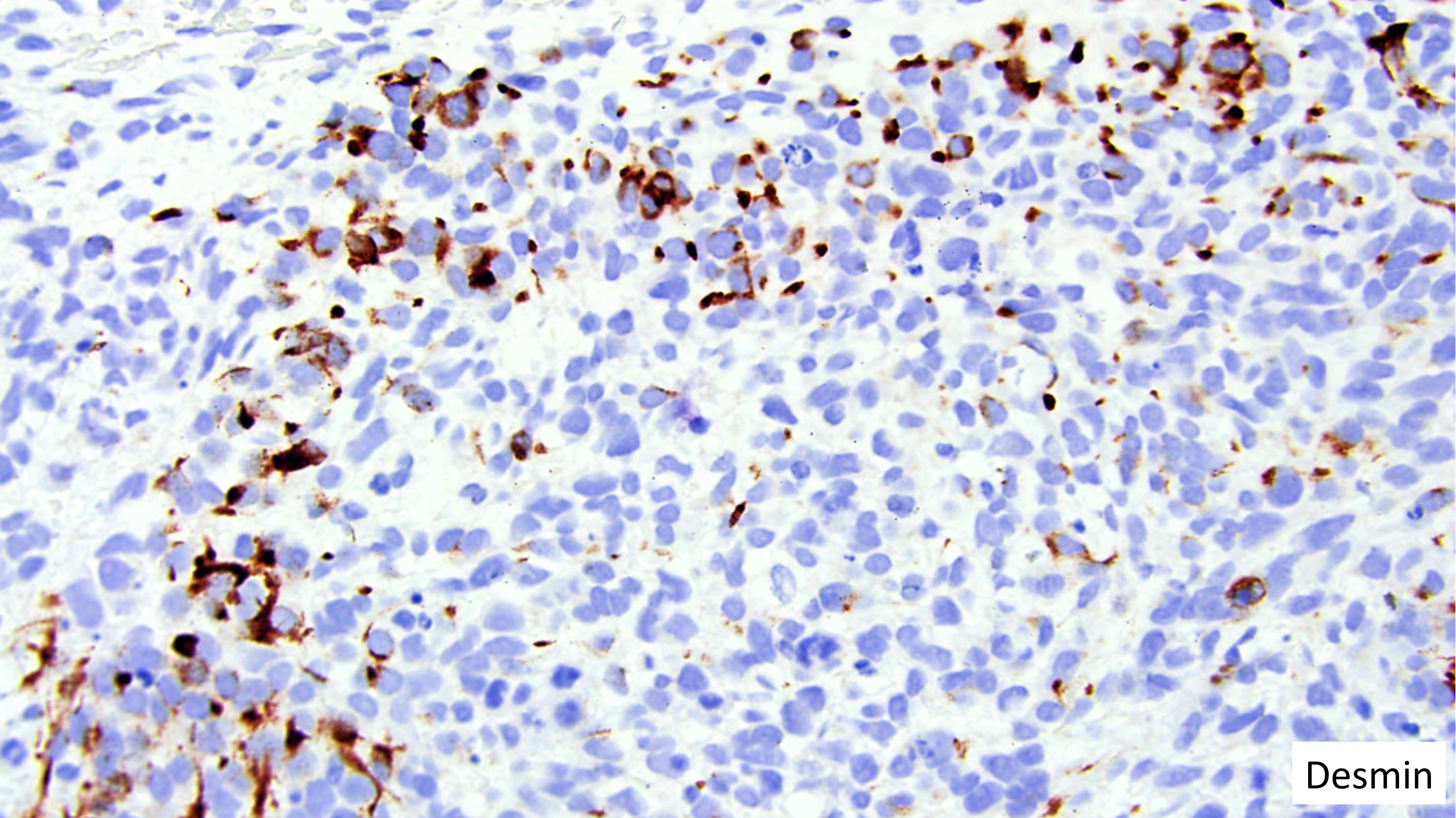
- 15-yo F with a known dx of NF1
- PF “diffuse infiltrating astrocytoma, WHO grade II” 11 years prior
- L parietal “poorly-differentiated high grade neoplasm, most c/w gliosarcoma, WHO grade IV” 4 years prior
- Now with recurrence at margin of resection cavity and dura






Reticulin


GFAP


Desmin

Initial Dx: Poorly differentiated neoplasm with features suggestive of gliosarcoma, CNS WHO grade 4, clinically recurrent

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
DICER1 p.G1809R	NM_177438	Pathogenic	1214	52%
DICER1 c.2436+1G>A	NM_177438	Pathogenic	924	42%
TP53 p.W91*	NM_000546	Pathogenic	164	93%
Elevated somatic mutation burden with ~40 somatic nonsynonymous mutation that are virtually all C>T/G>A transitions corresponding to Mutational Signature 11 that occurs after alkylating chemotherapy	N/A	Pathogenic	N/A	N/A
NF1 p.D2632G	NM_001042492	Likely Pathogenic	968	60%

'Reads' indicate the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

Pathogenic or Likely Pathogenic GERMLINE ALTERATIONS*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
NF1 c.574C>T, p.R192*	NM_001042492	Pathogenic	206/712	50%/38%

*Germline variants are reported if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist. For variants not classified in ClinVar, truncating variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Germline variants are limited to single nucleotide variants and small indels in gene coding regions.

Final Dx: Primary intracranial sarcoma, *DICER1*-mutant, clinically recurrent

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Primary intracranial sarcoma, *DICER1*-mutant

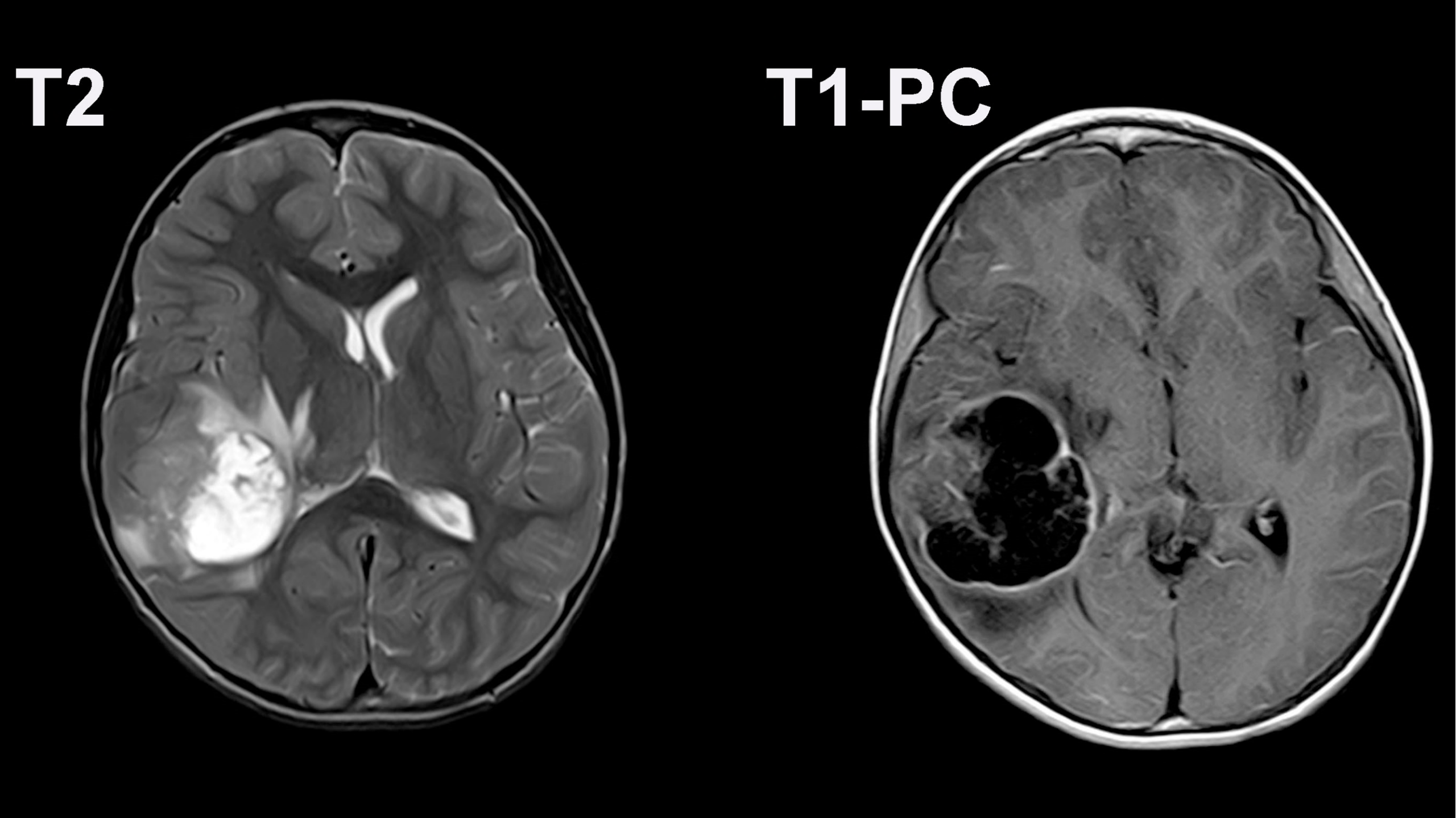
- New WHO sarcoma type with inactivation of *DICER1* gene
- Somatic or germline (mostly DICER1 syndrome, but rare NF1)
- Pleomorphic spindled to primitive small round blue cells, often with prominent eosinophilic granules
- May have limited myogenic and/or chondroid differentiation
- Mimicry of astrocytic neoplasms includes focal infiltration, ATRX loss, p53 overexpression, H3K27me3 loss

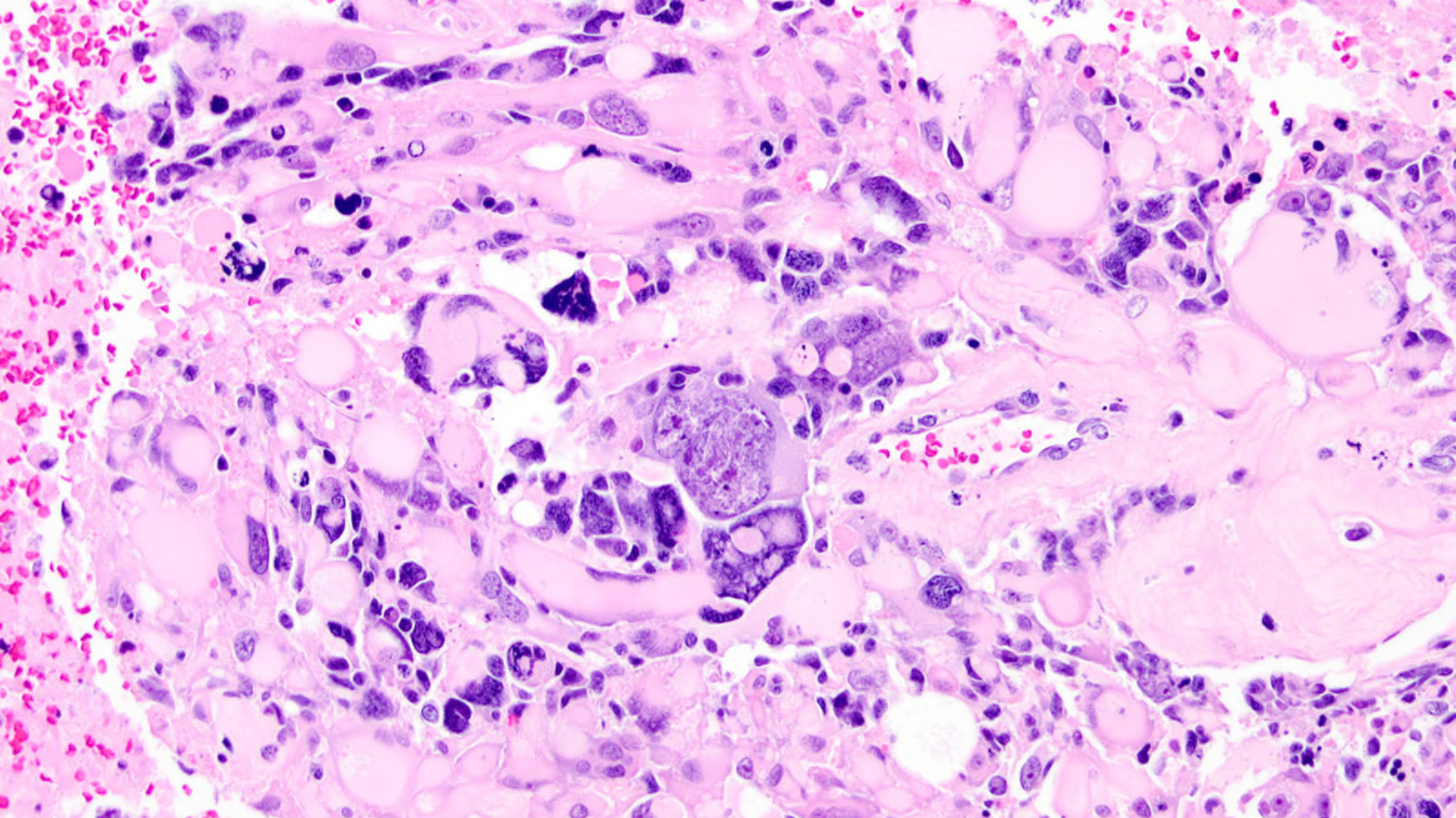
DICER1 Syndrome: CNS manifestations

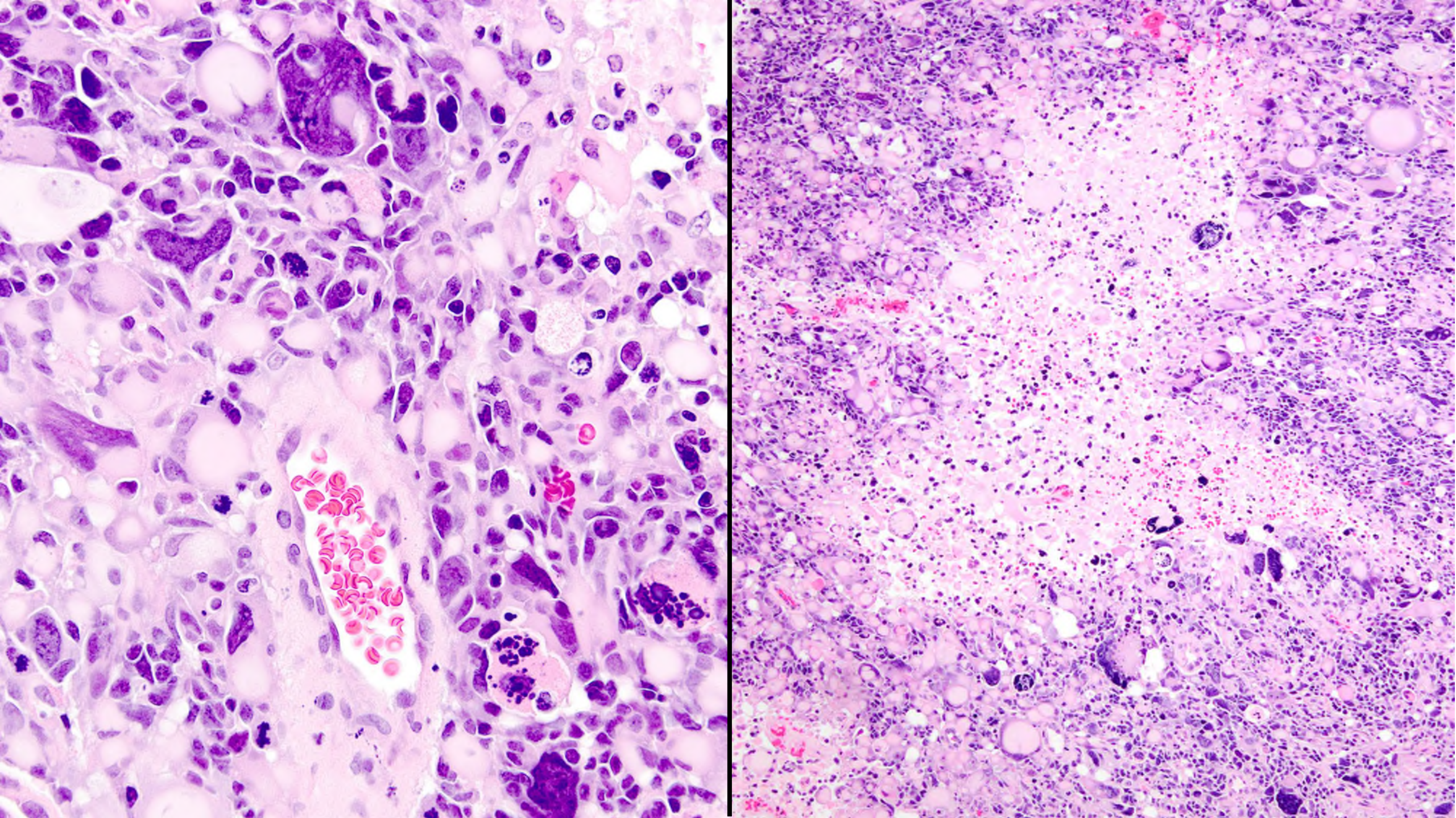
- Metastatic PPB
- Primary intracranial sarcoma, *DICER1*-mutant
- Pineoblastoma
  - miRNA processing-altered molecular groups
- ETMR, *DICER1*-mutant
- Pituitary blastoma
- Ciliary body medulloepithelioma

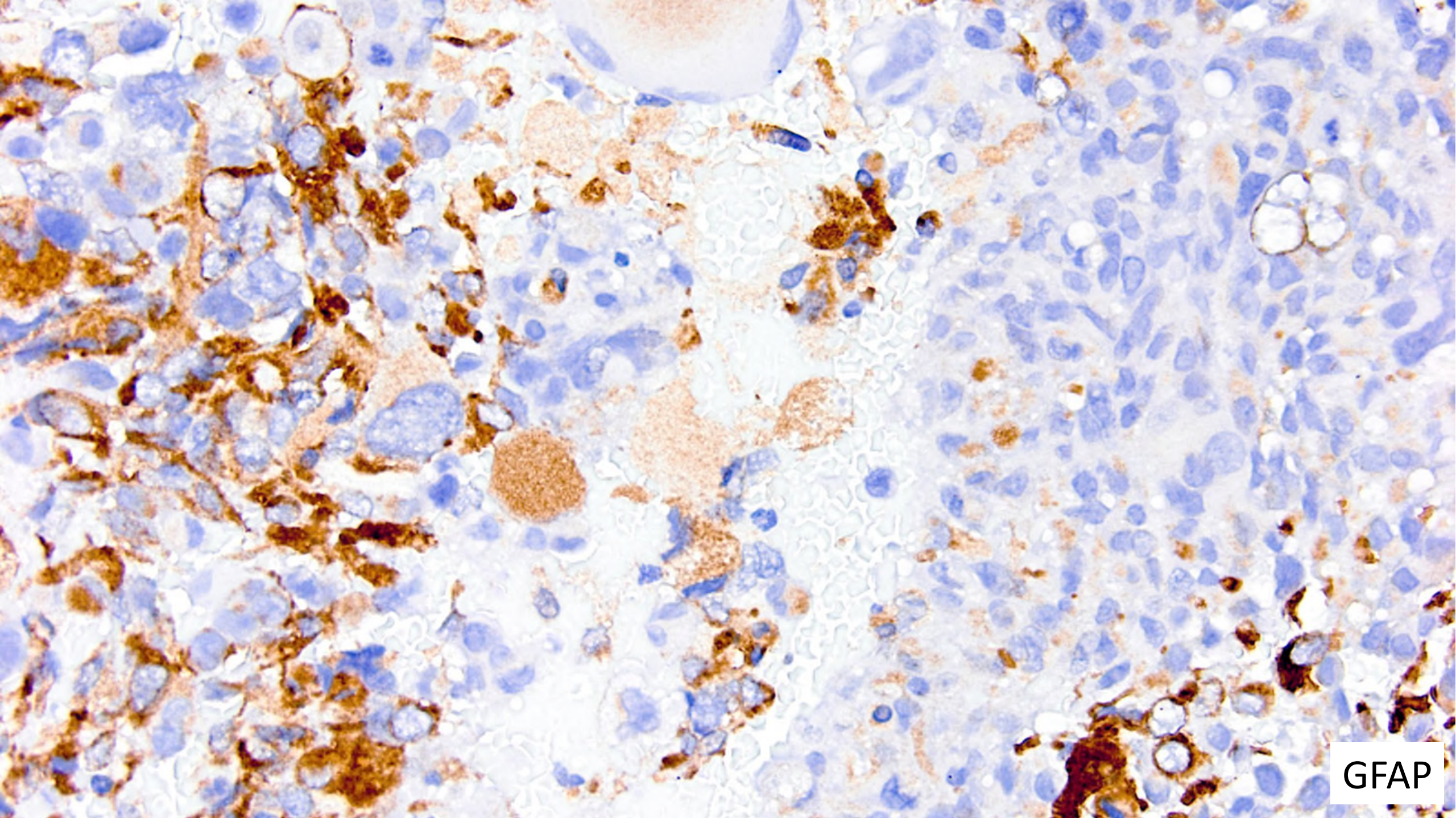
CASE 6

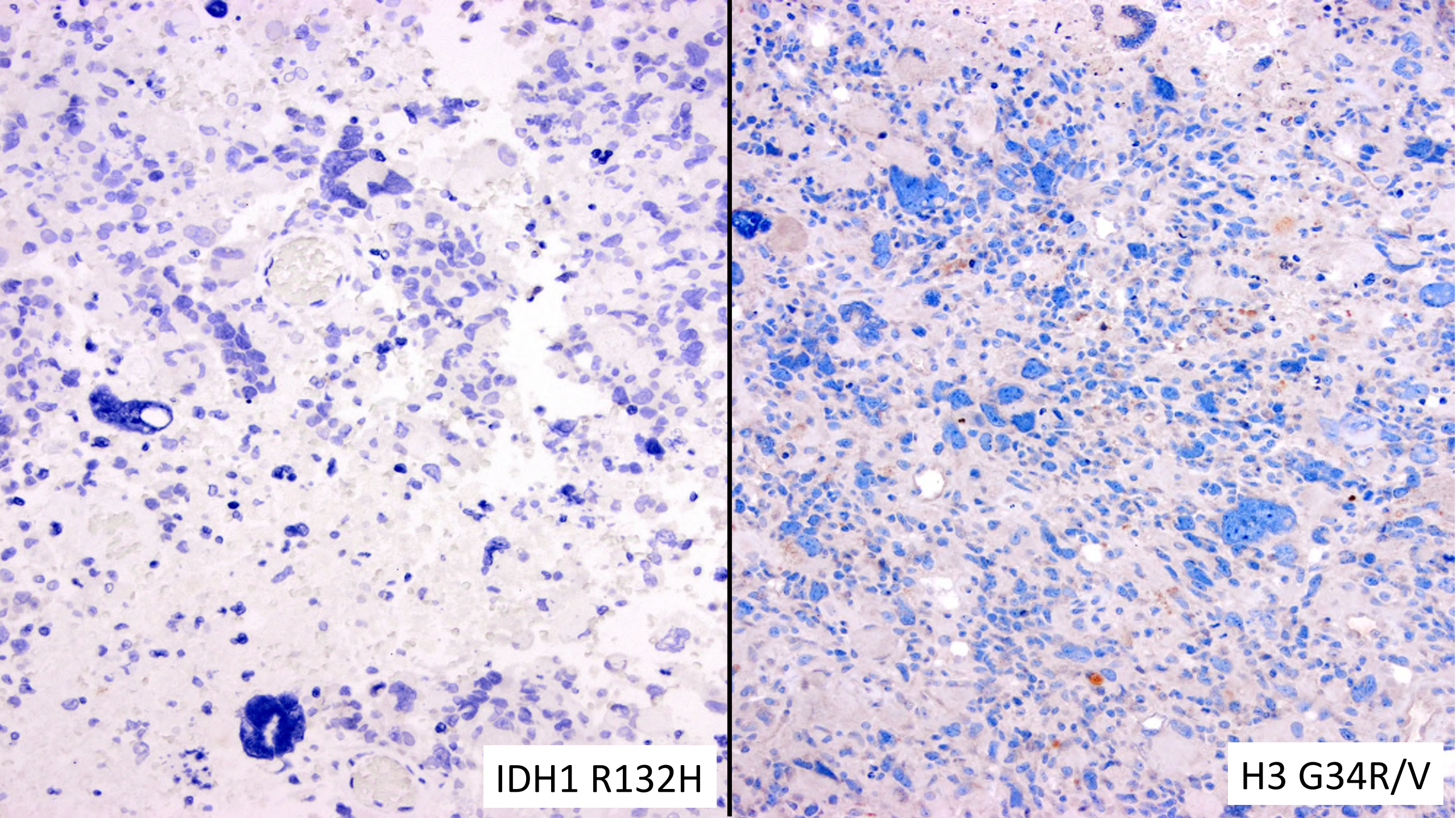
- 9-yo M
- 2-3 weeks of headaches, N/V
- MRI: 5.4 cm solid and cystic right temporal lobe mass

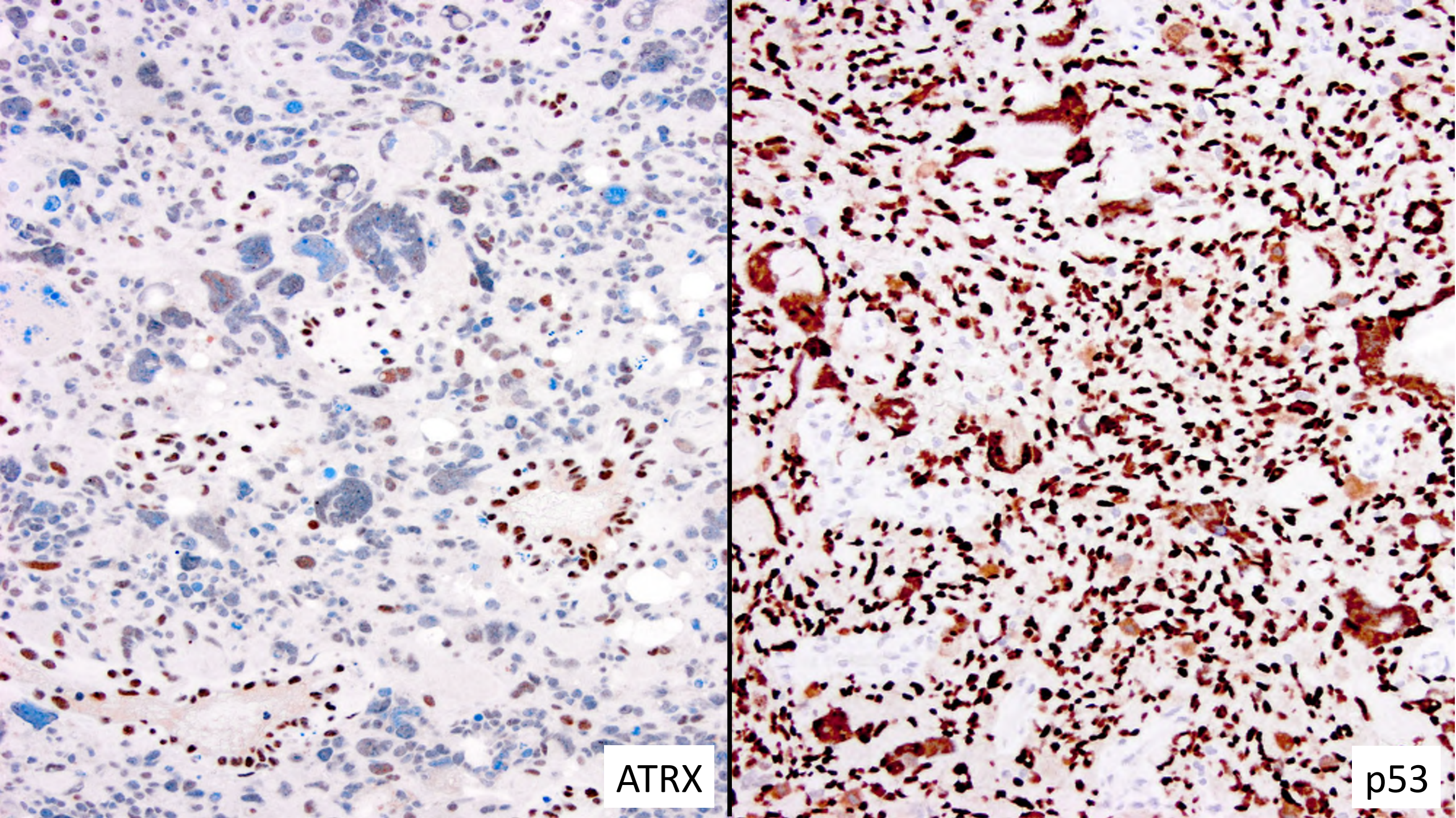

T2
T1-PC

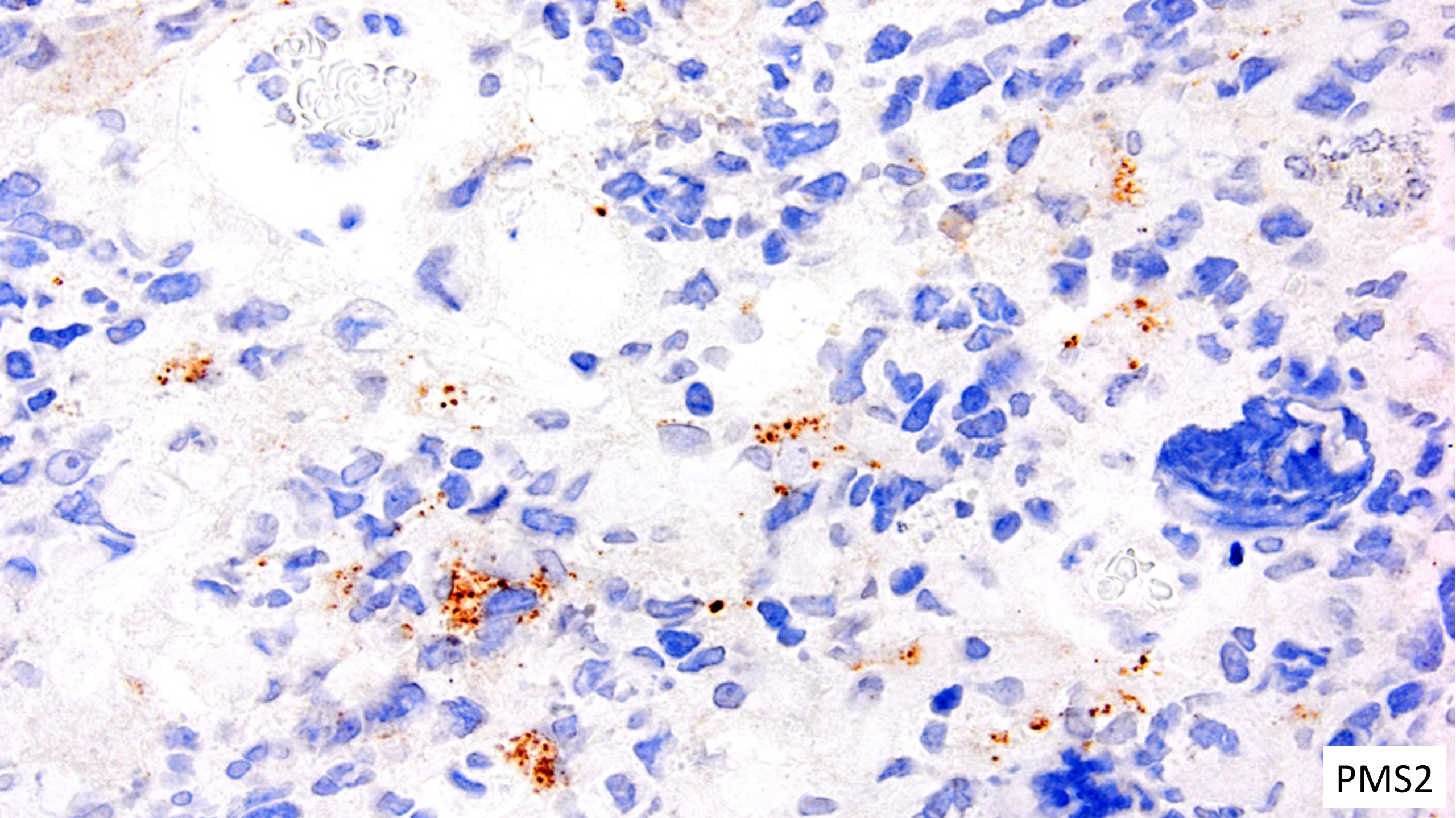





GFAP


IDH1 R132H
H3 G34R/V


ATRX
p53


PMS2

SELECTED SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
Microsatellite unstable tumor with instability at 15% of evaluated microsatellites	N/A	Pathogenic	N/A	N/A
Extremely high somatic mutation burden consistent with "ultrahypermutation", with a predominance of C>T transitions, C>A transversions, and small indels corresponding with a combination of Mutational Signature 6 associated with defective mismatch repair and Mutational Signature 10 associated with altered activity of the DNA polymerase POLE	N/A	Pathogenic	N/A	N/A
ATRX p.L648fs	NM_000489.3	Pathogenic	562	97%
CREBBP c.3836+1G>A	NM_004380.2	Pathogenic	874	7%
EGFR p.T790M	NM_005228.3	Pathogenic	511	3%
ERRFI1 p.R199*	NM_018948.3	Pathogenic	1288	47%
HRAS p.G12D	NM_005343.2	Pathogenic	214	45%
KMT2D p.R4904*	NM_003482.3	Pathogenic	377	10%
NF1 p.V472fs	NM_001042492.2	Pathogenic	154	45%
NF1 c.4430+1G>A	NM_001042492.2	Pathogenic	714	48%
POLE p.S459Y	NM_006231.2	Pathogenic	429	46%
PTPN11 p.R498W	NM_002834.3	Pathogenic	325	46%
SETD2 p.E2402*	NM_014159.6	Pathogenic	751	48%
SETD2 c.5142+1G>A	NM_014159.6	Pathogenic	879	44%
TP53 p.E258K	NM_000546.5	Pathogenic	345	50%
TP53 p.R248W	NM_000546.5	Pathogenic	386	48%
TP53 p.C124*	NM_000546.5	Pathogenic	256	23%
TSC2 p.R1138*	NM_000548.3	Pathogenic	205	42%

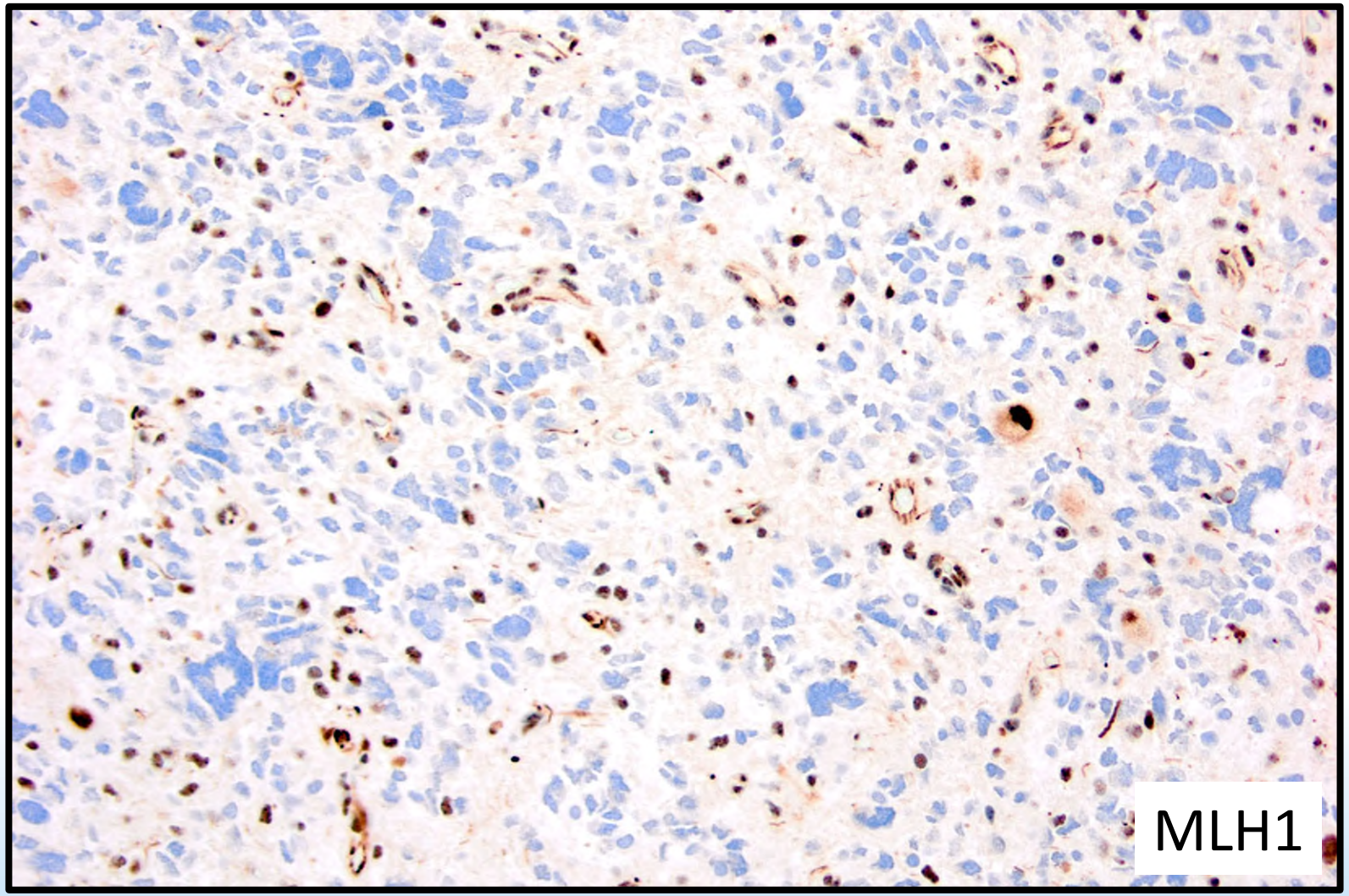
*More than 50 non-synonymous somatic mutations are present. See interpretation and see appendix for list of additional variants.

Pathogenic or Likely Pathogenic ALTERATIONS IN THE NORMAL SAMPLE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS (Normal/Tumor)**	**MUTANT ALLELE FREQUENCY (Normal/Tumor)**
PMS2 intragenic deletion of 3' coding exons (heterozygous/one copy)	NM_000535	Pathogenic	N/A	N/A
PMS2 c.353+2T>C	NM_000535	Pathogenic	86/138	49%/47%

*Alterations in the normal sample are reported for cancer-related genes if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist. For variants not classified in ClinVar, truncating or splice-site variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Alterations in the normal sample are limited to single nucleotide variants and small indels in gene coding regions. Carrier status is not reported for variants not strongly related to cancer.

Final Dx: Diffuse pediatric-type HGG with giant cell features, H3-wildtype and IDH-wildtype, arising in the setting of constitutional mismatch repair defect syndrome, CNS WHO grade 4

Similar example in FAP1 (Lynch syndrome)



CMMRD

- Autosomal recessive (Lynch syndrome autosomal dominant)
- Biallelic germline inactivation of MMR gene (heterozygous variant in Lynch syndrome)
- Parental consanguinity common
- Cutaneous café-au-lait macules causes confusion with NF1
- GI polyposis/cancers (100%), T-cell leukemia/lymphoma (30%), and less often, soft tissue sarcomas and GU cancers
- Ultra-hypermutation genotype (>100 mutations per mb) due to MMR plus POLE or POLD deficiency
- CMMRD pts c HGG now treated with immune checkpoint blockade

Not covered

14.0.0.15: Familial paraganglioma syndromes
14.0.0.16: Melanoma-astrocytoma syndrome
14.0.0.17: Familial retinoblastoma
14.0.0.18: BAP1 tumour predisposition syndrome
14.0.0.19: Fanconi anaemia
14.0.0.20: ELP1-medulloblastoma syndrome

Conclusions

- A growing number of hereditary tumor syndromes with CNS and/or PNS involvement are being recognized
- The neuropathologist often gets some of the first clues and therefore, plays a critical role in diagnosis of the syndrome
- Further clinical workup, germline testing, and/or referral to a genetic counselor should be recommended in such cases

THANK YOU!