NF1-associated nervous system tumors

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Johns Hopkins University School of Medicine

Disclosures

- I have the following relevant financial relationships to disclose:
  - Consultant, *Servier Pharmaceuticals*

Learning Objectives

1. Outline updated molecular diagnostic criteria for NF1-associated central and peripheral nervous system tumors

2. Differentiate “low grade” from “high grade” pathologies

3. Identify appropriate ancillary tests (IHC, NGS, methylation profiling) for real-world cases

NF1 – autosomal dominant tumor predisposition syndrome caused by loss of RAS pathway control

- **Genetics**
- *NF1* gene (chr 17q11.2)
- Loss-of-function mutations
- Autosomal dominant
- ~50% de novo

- **Pathophysiology**
- Neurofibromin = RAS pathway inhibitor
- NF1 loss → ↑ RAS/MAPK signaling → tumorigenesis

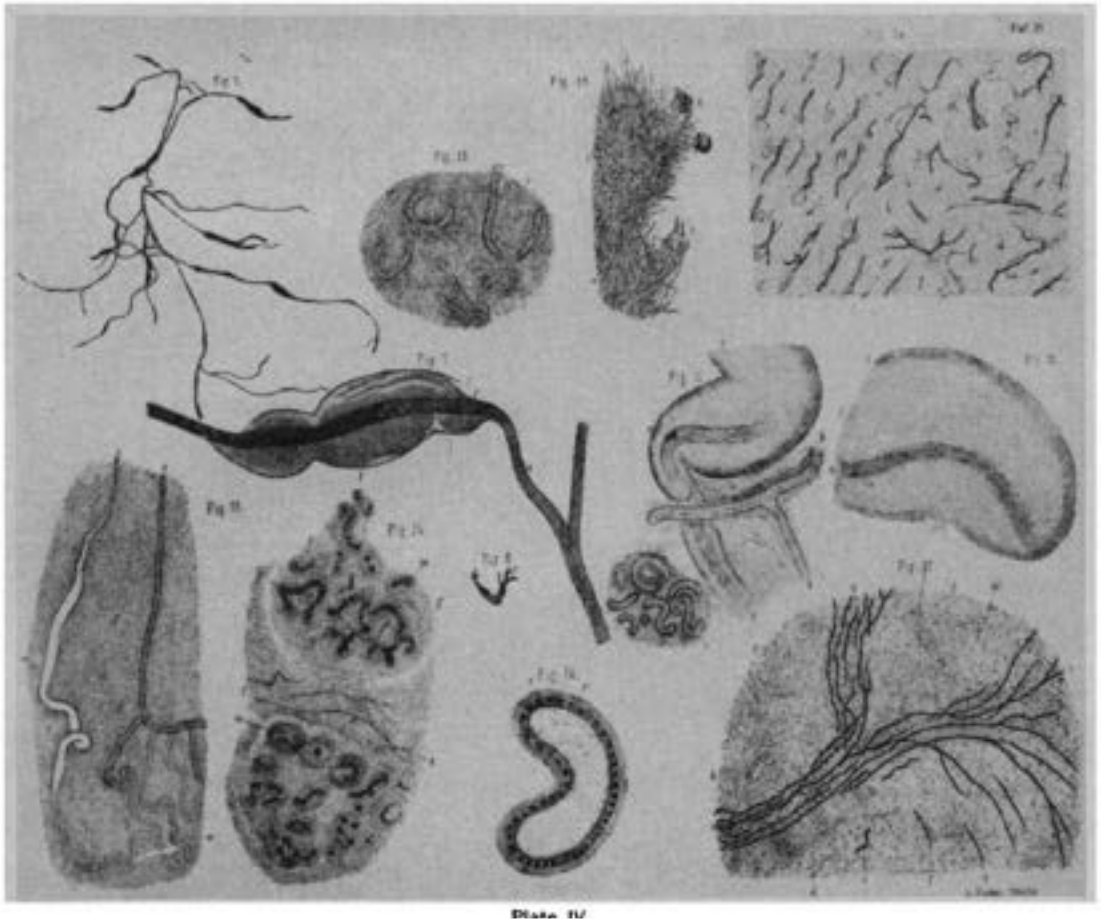
- **Clinical implications**
- Tumor predisposition
- Multidisciplinary surveillance required
- Targeted therapy: MEK inhibitors (e.g., selumetinib)

- **Clinical features**
- ≥6 café-au-lait macules
- Axillary/inguinal freckling
- Lisch nodules (iris)

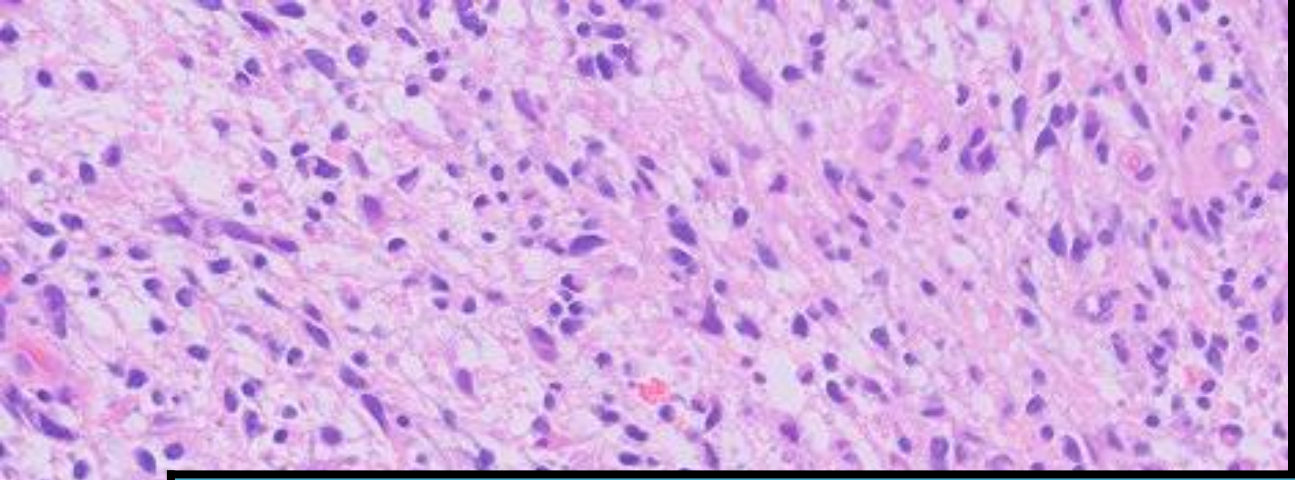
AANP

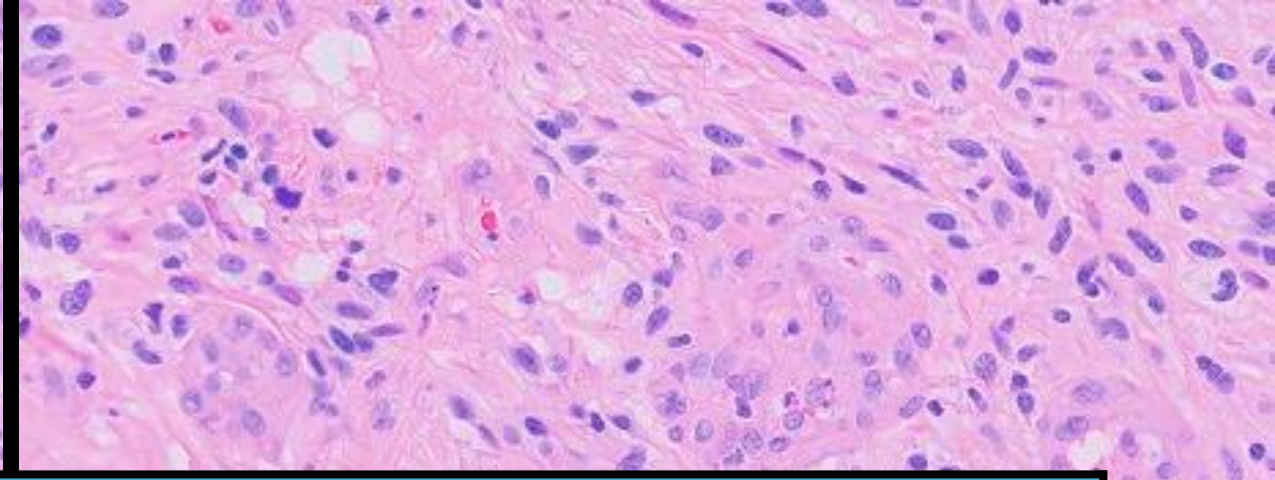
Concerning Multiple Fibromas of the Skin and Their Relationship to Multiple Neuromas*

by F. v. Recklinghausen
Professor in Strassburg

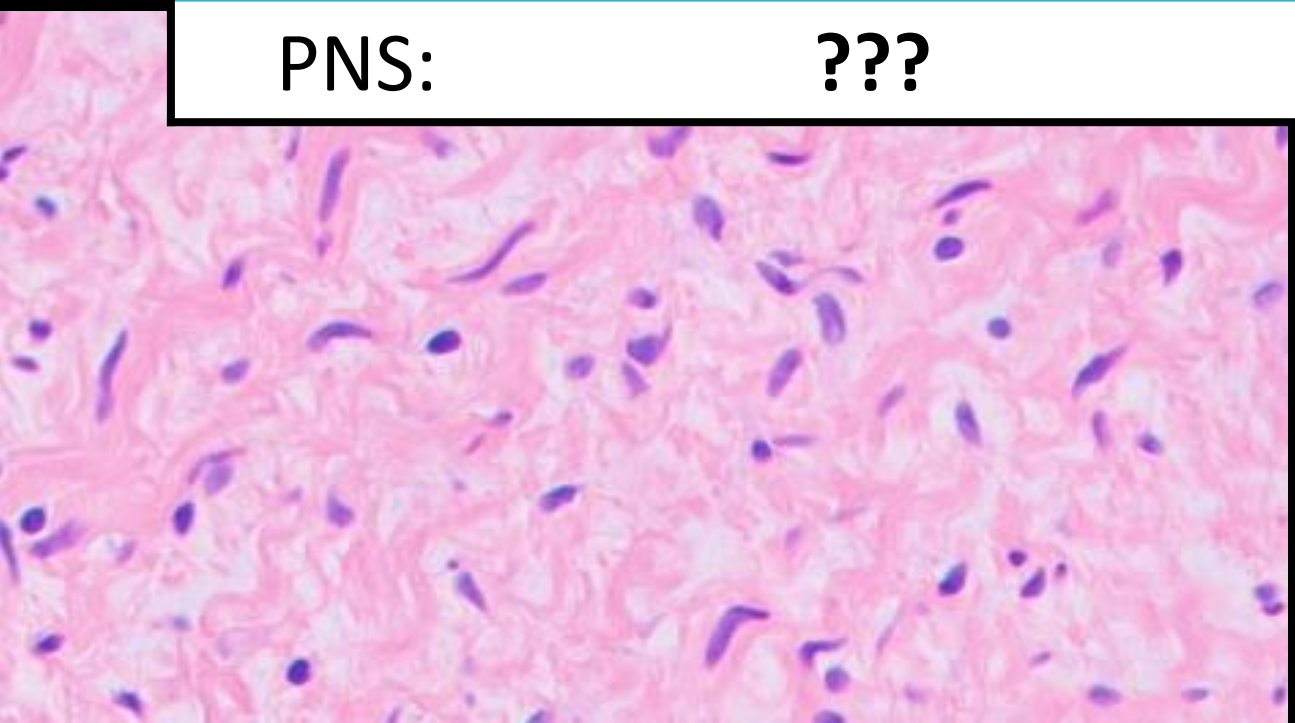


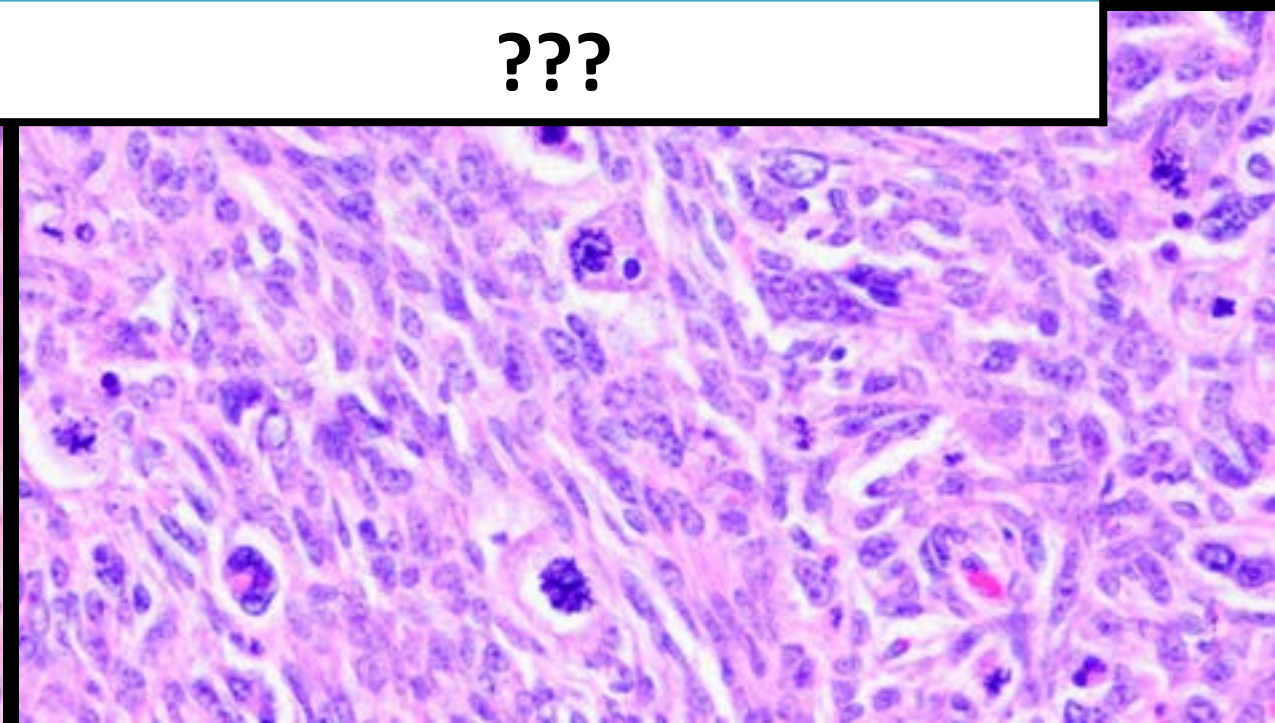
Recklinghausen FV. *1882*.

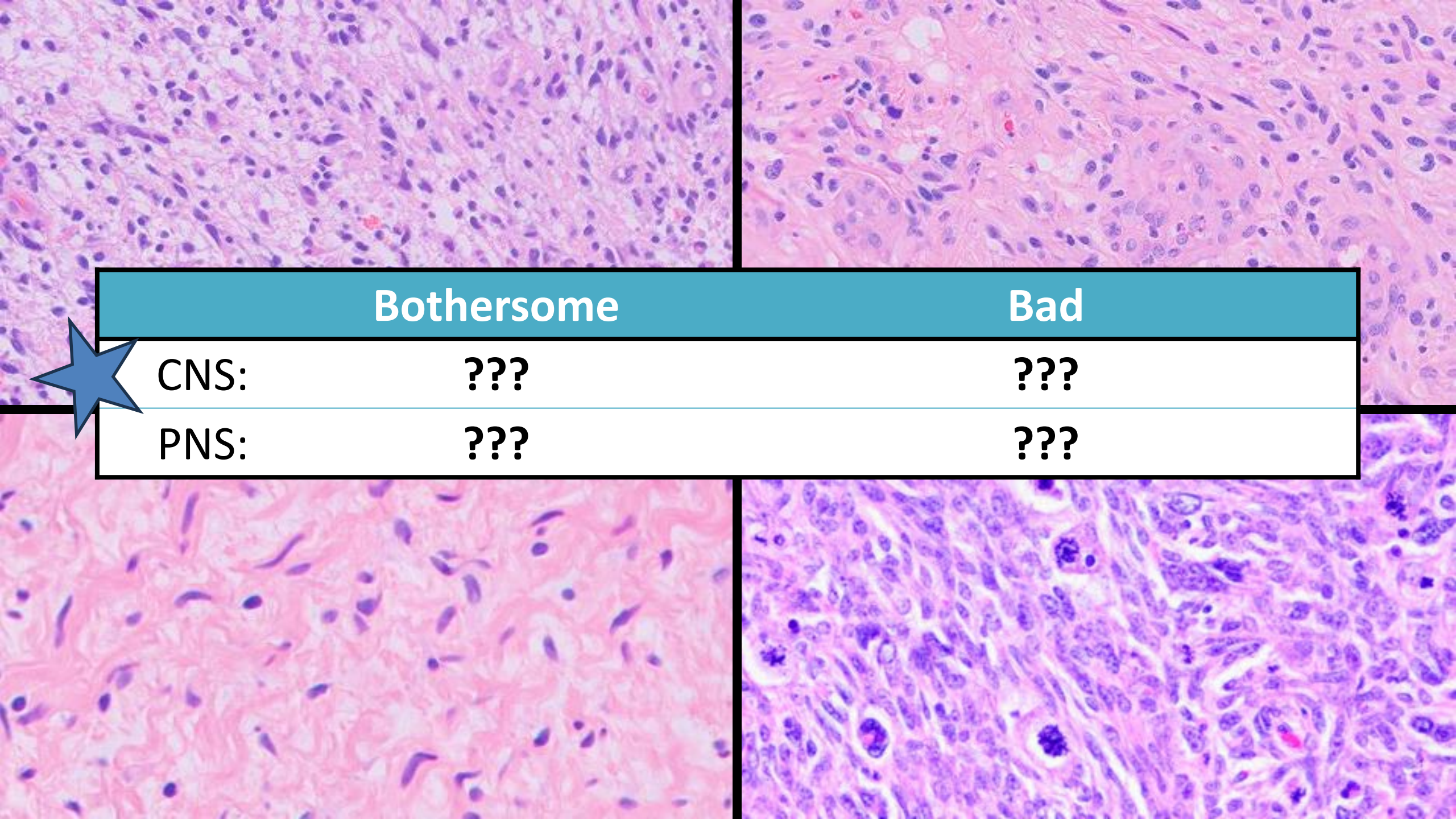




	Bothersome	Bad
CNS:	???	???
PNS:	???	???







	Bothersome	Bad
CNS:	???	???
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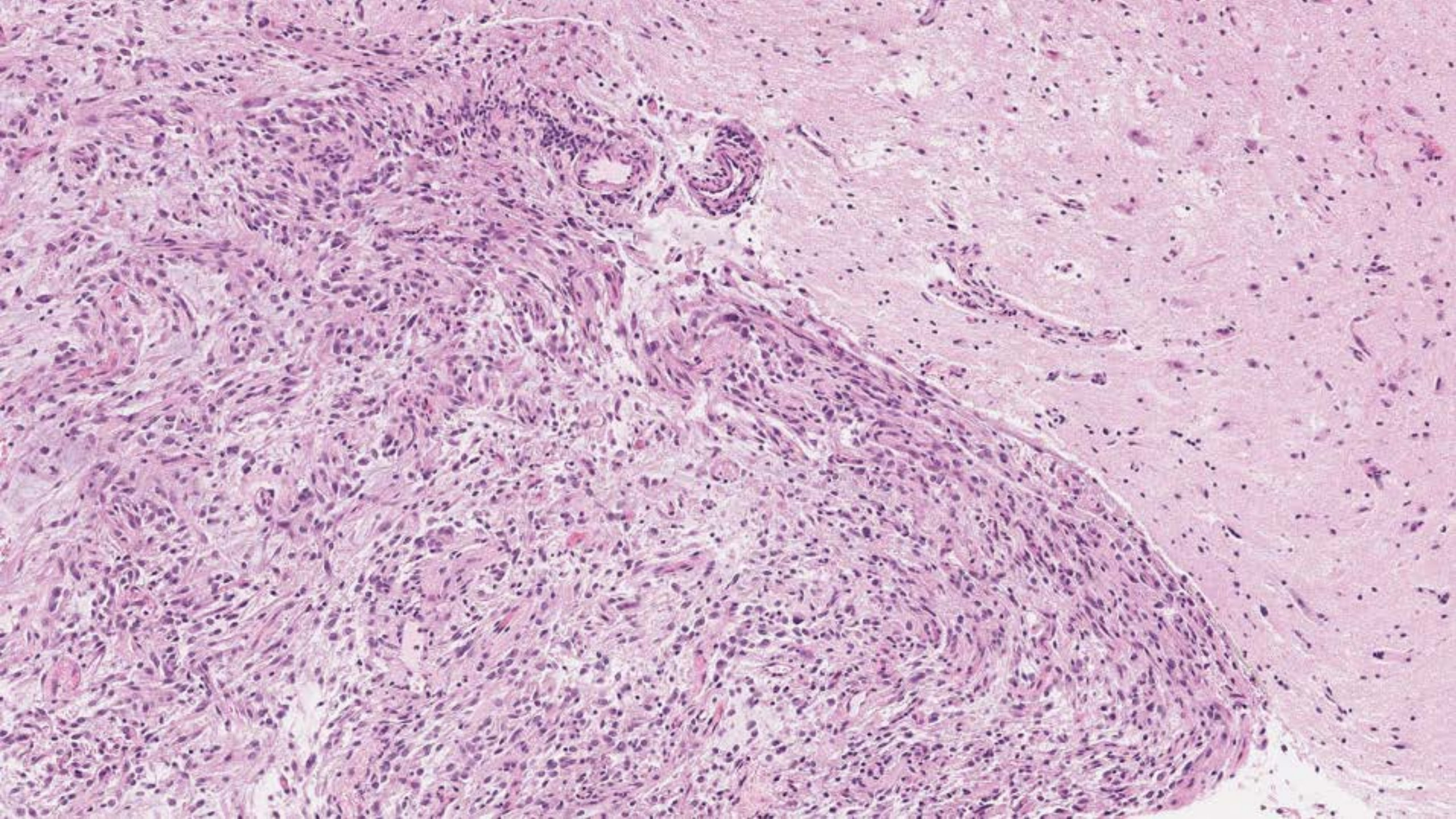
Gliomas arising in the setting of NF1 are heterogeneous

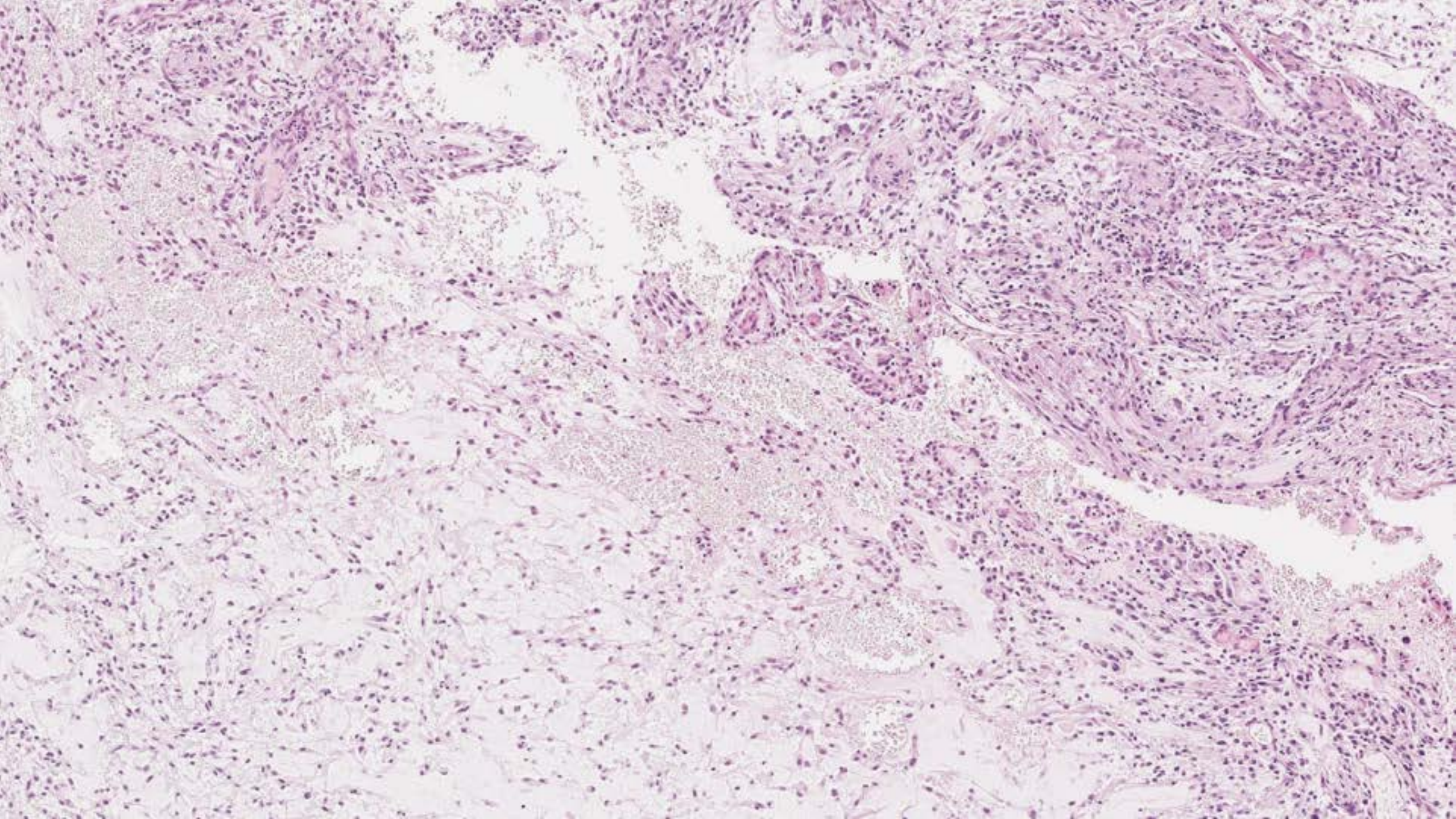
- Occur from childhood through adulthood
- Can be histologically low-grade or high-grade
- May follow an indolent or aggressive clinical course

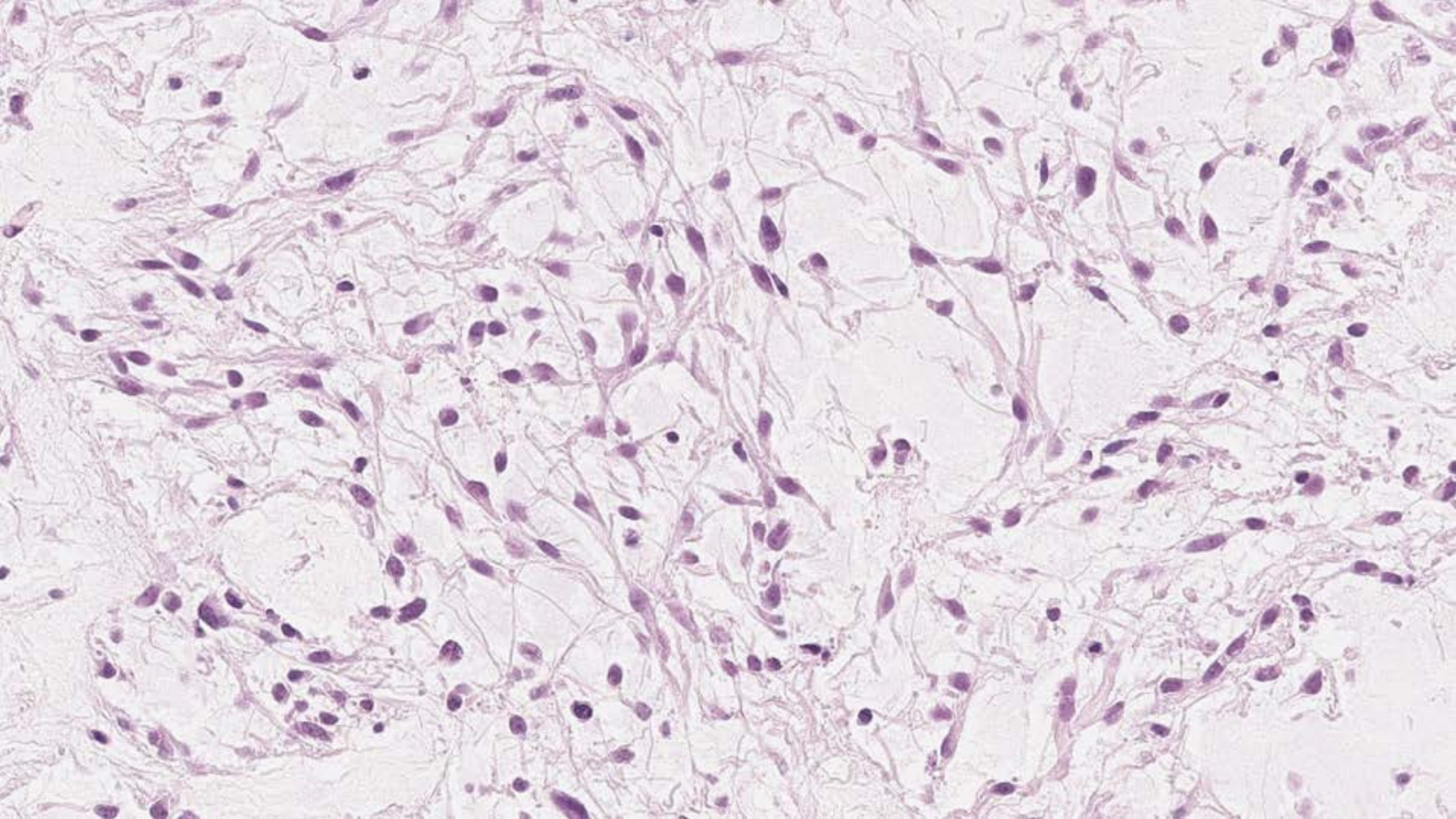
- Comprehensive profiling of genetic alterations beyond *NF1* and epigenetic classification of these tumors remain relatively limited

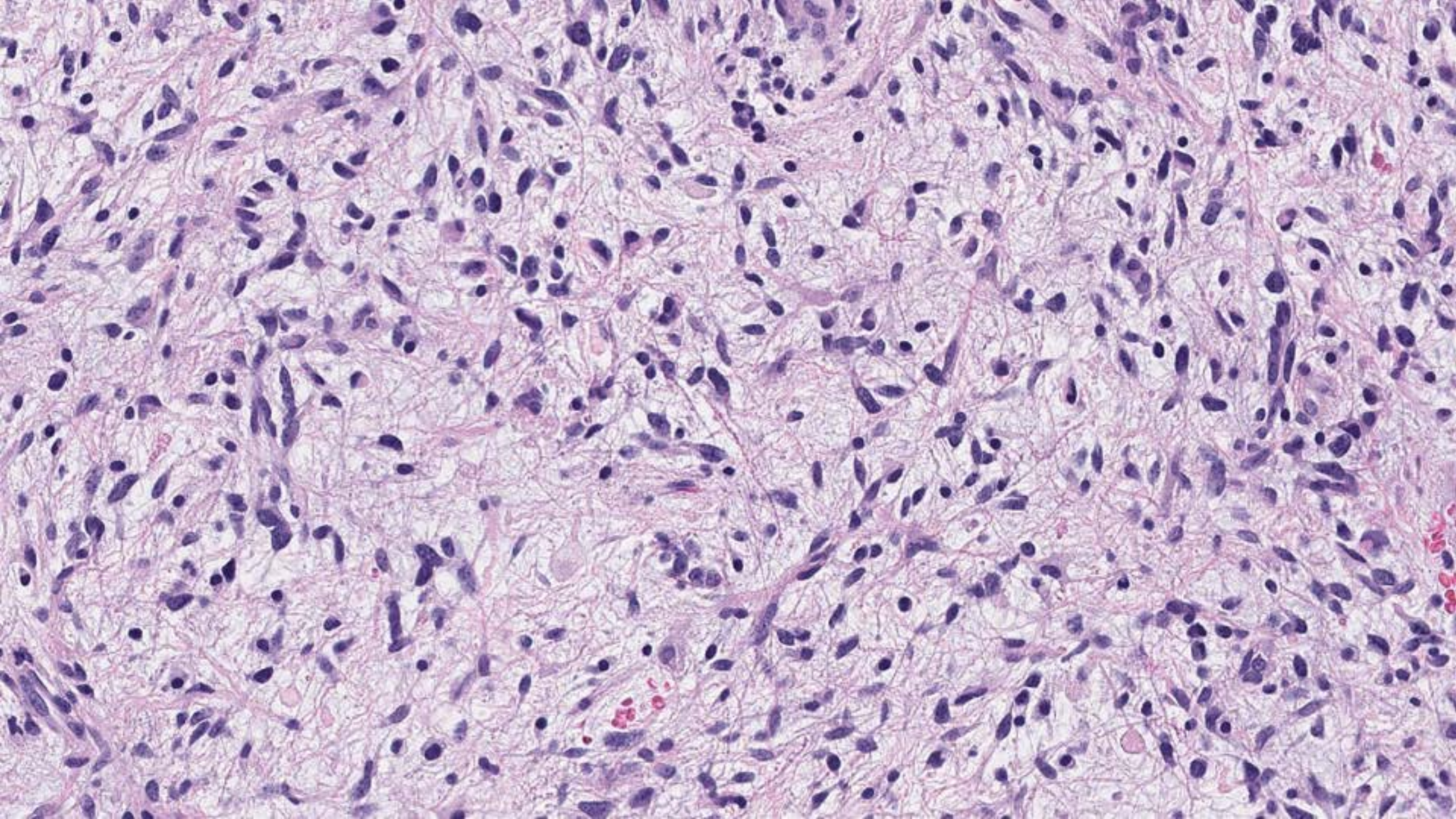
Case 1

- 12-year-old boy with staring and lip-smacking episodes
- Diagnosed with NF1 at age 5 (multiple café-au-lait macules, axillary freckling, and Lisch nodules, mother also has NF1)
- Right temporal epileptiform discharges
- Well-circumscribed mixed cystic and solid lesion of the right temporal lobe, mural nodule demonstrates avid enhancement
- Undergoes resection

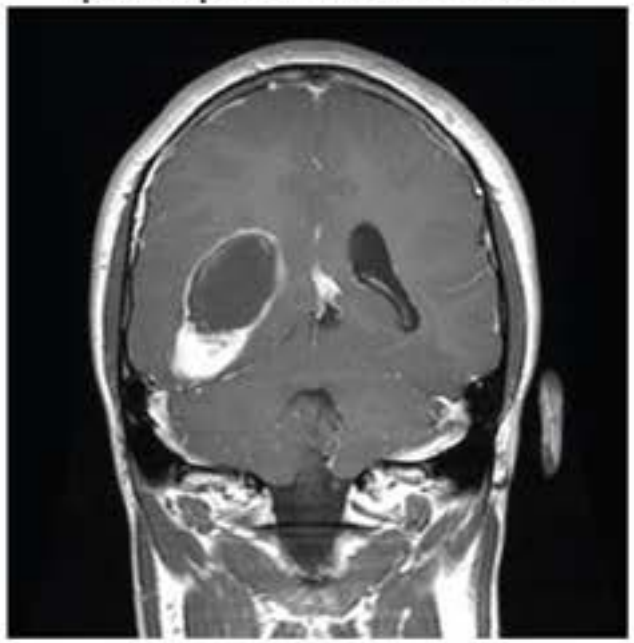




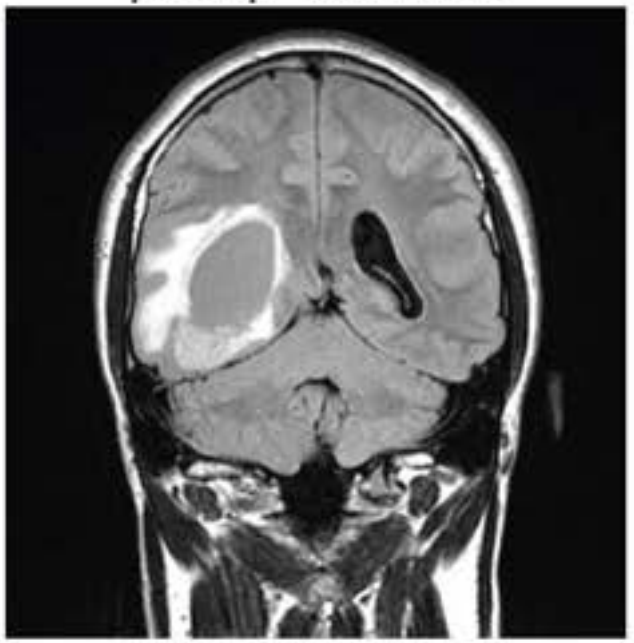


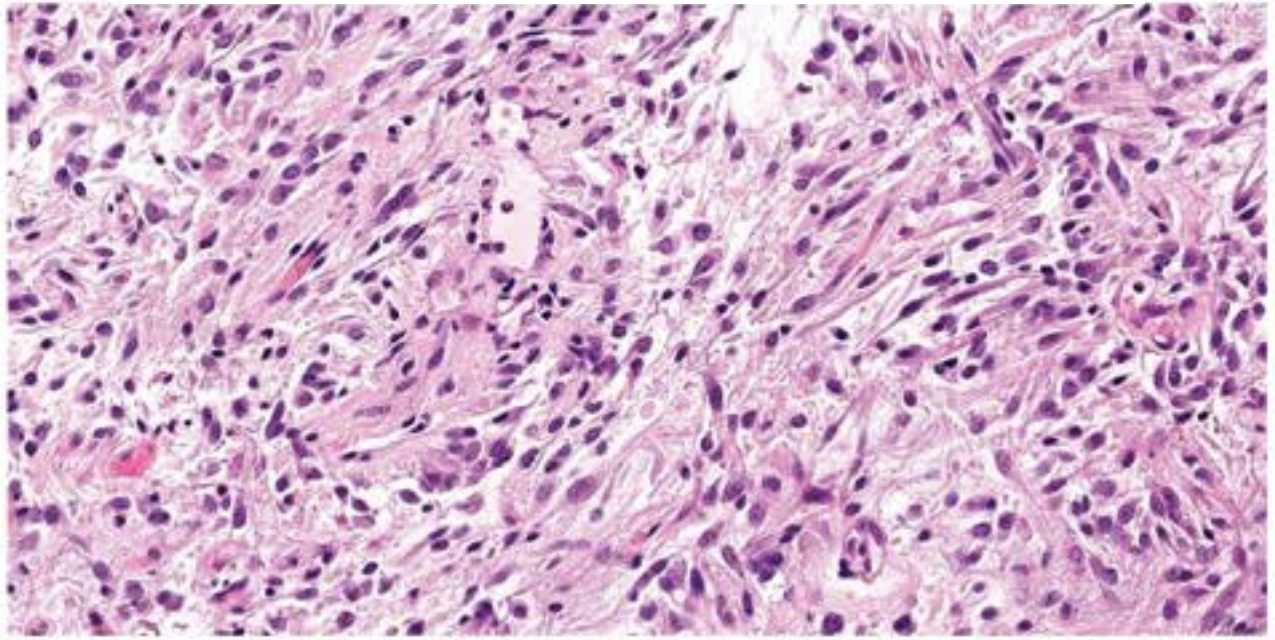


pre-op T1 w/ contrast

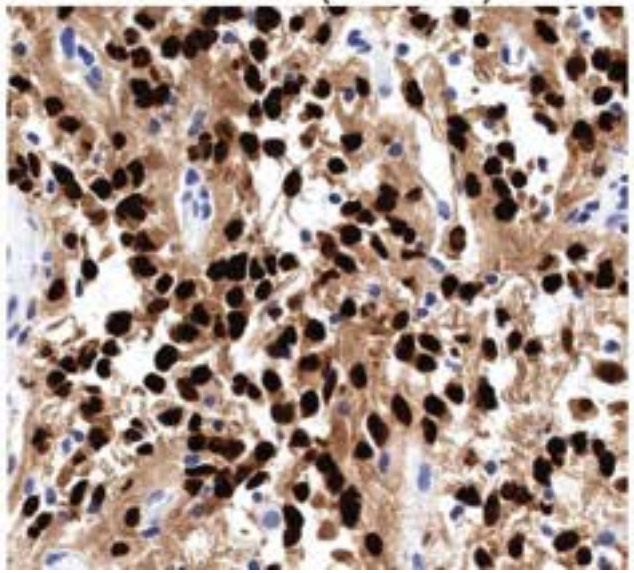


pre-op T2/FLAIR

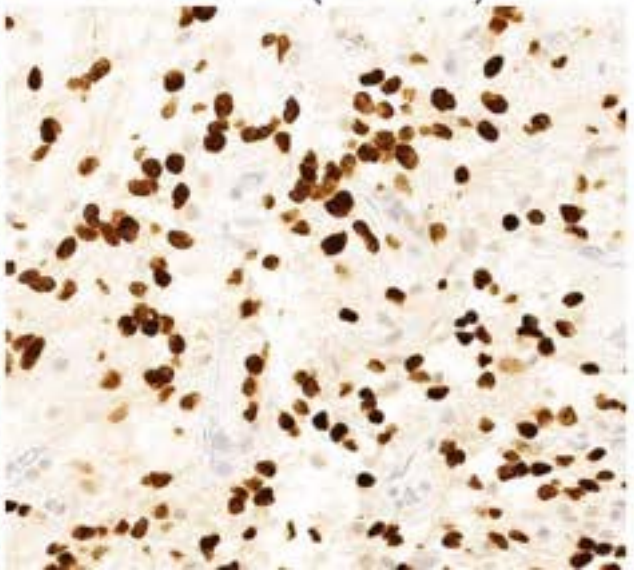




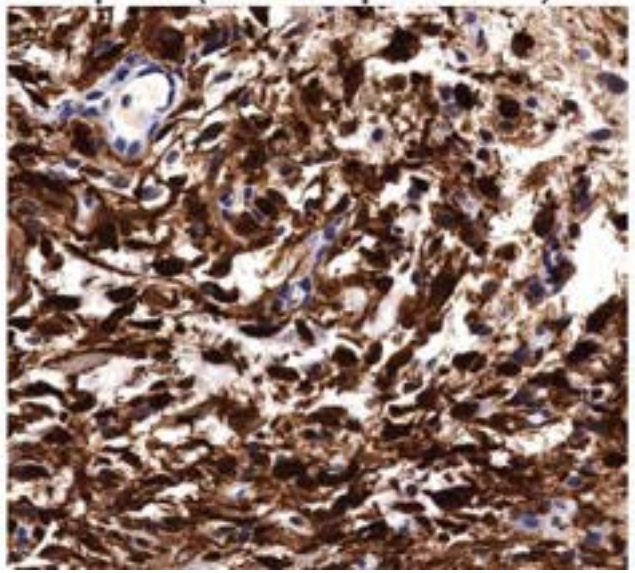
SOX10 (diffuse)



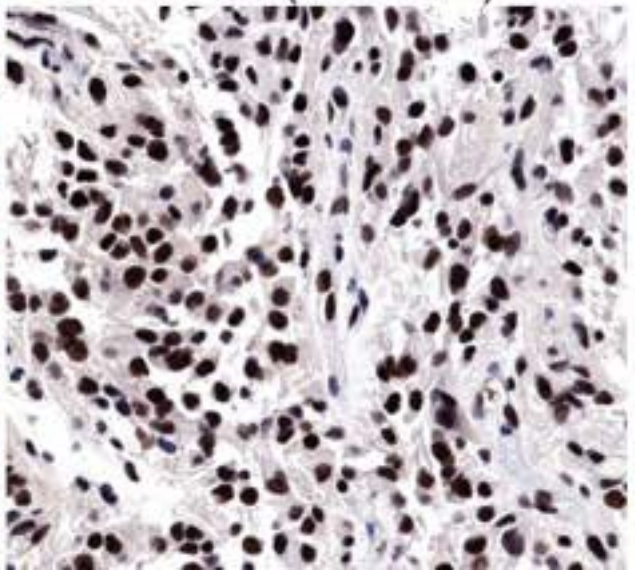
OLIG2 (diffuse)

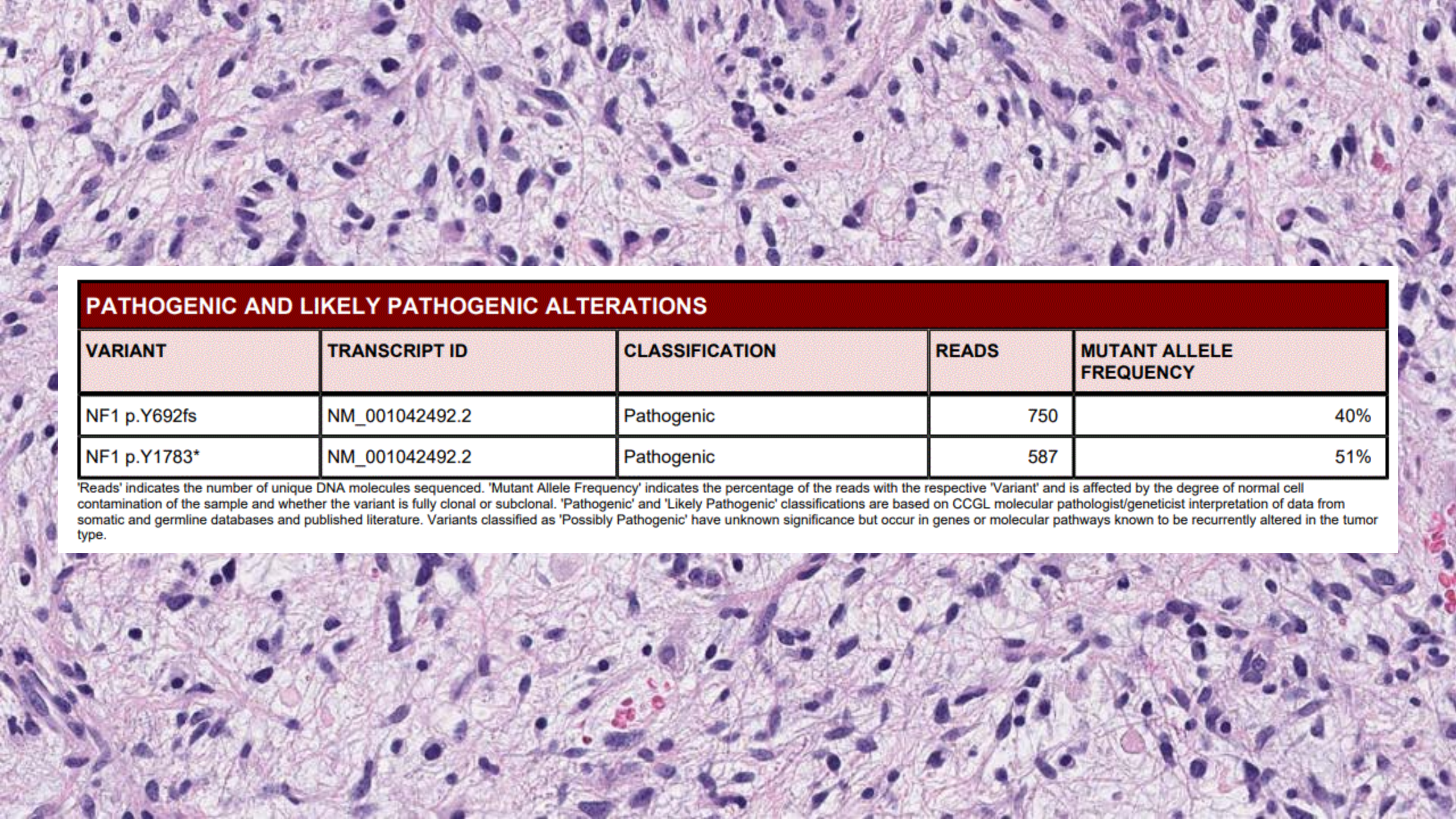


p16 (overexpressed)



ATRX (retained)





PATHOGENIC AND LIKELY PATHOGENIC ALTERATIONS

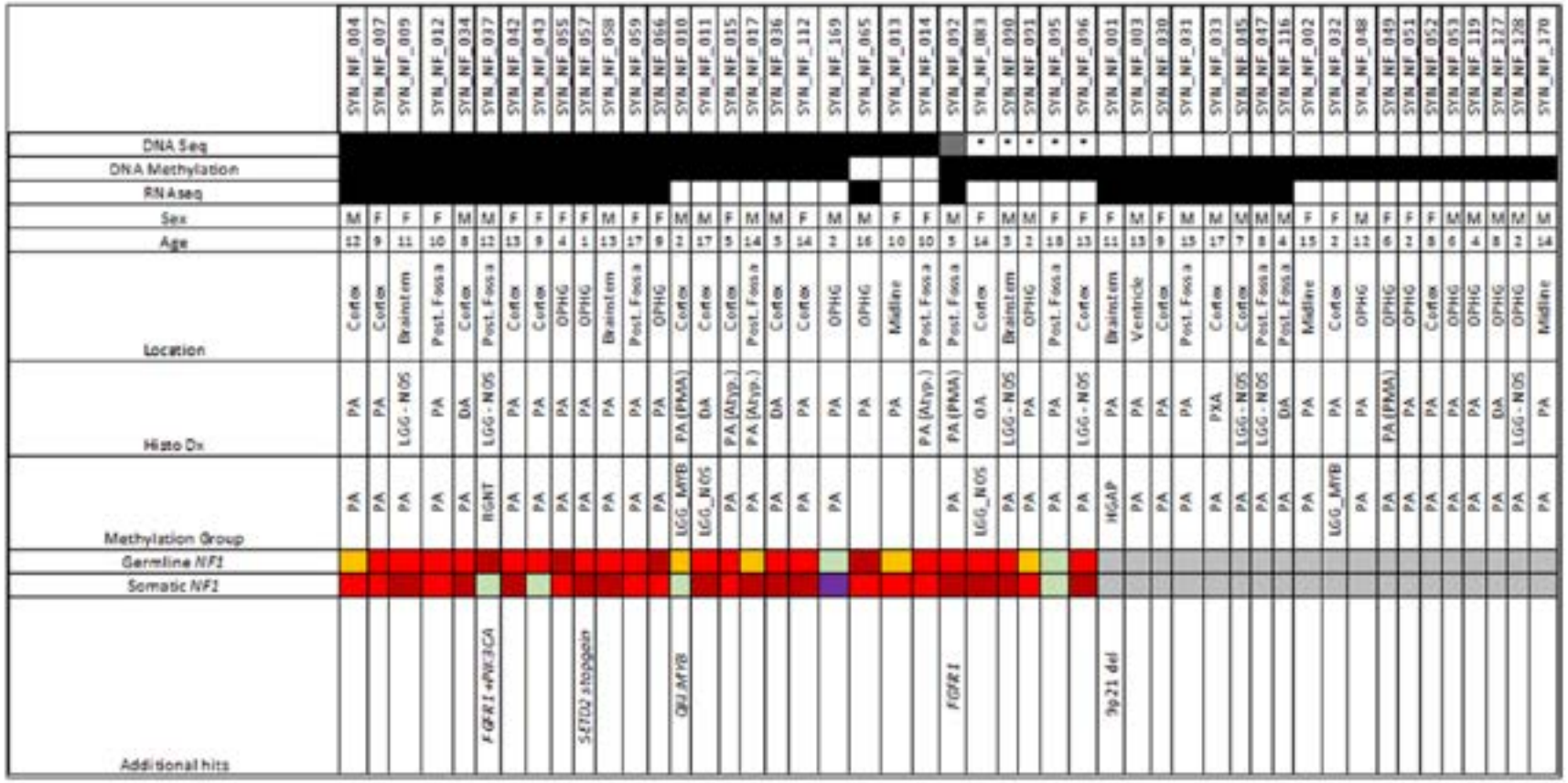
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
NF1 p.Y692fs	NM_001042492.2	Pathogenic	750	40%
NF1 p.Y1783*	NM_001042492.2	Pathogenic	587	51%

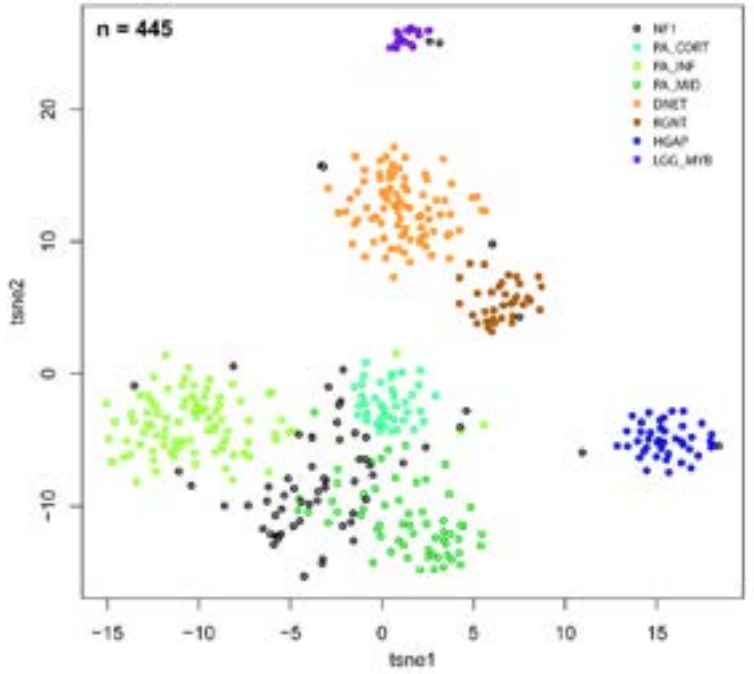
'Reads' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal. 'Pathogenic' and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

Acta Neuropathologica (2021) 141:605–617
https://doi.org/10.1007/s00401-021-02276-5

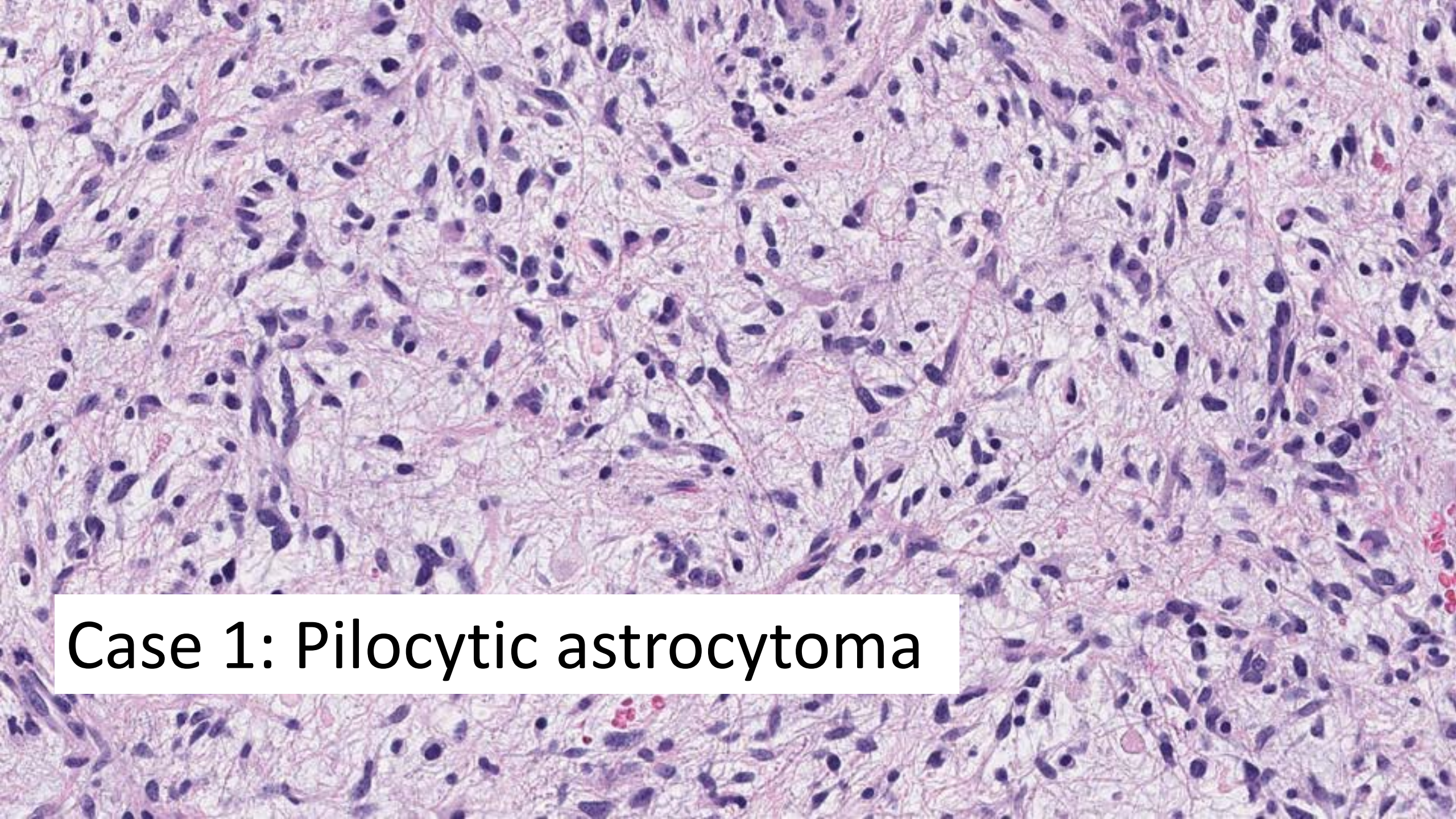
ORIGINAL PAPER

Integrated molecular and clinical analysis of low-grade gliomas in children with neurofibromatosis type 1 (NF1)





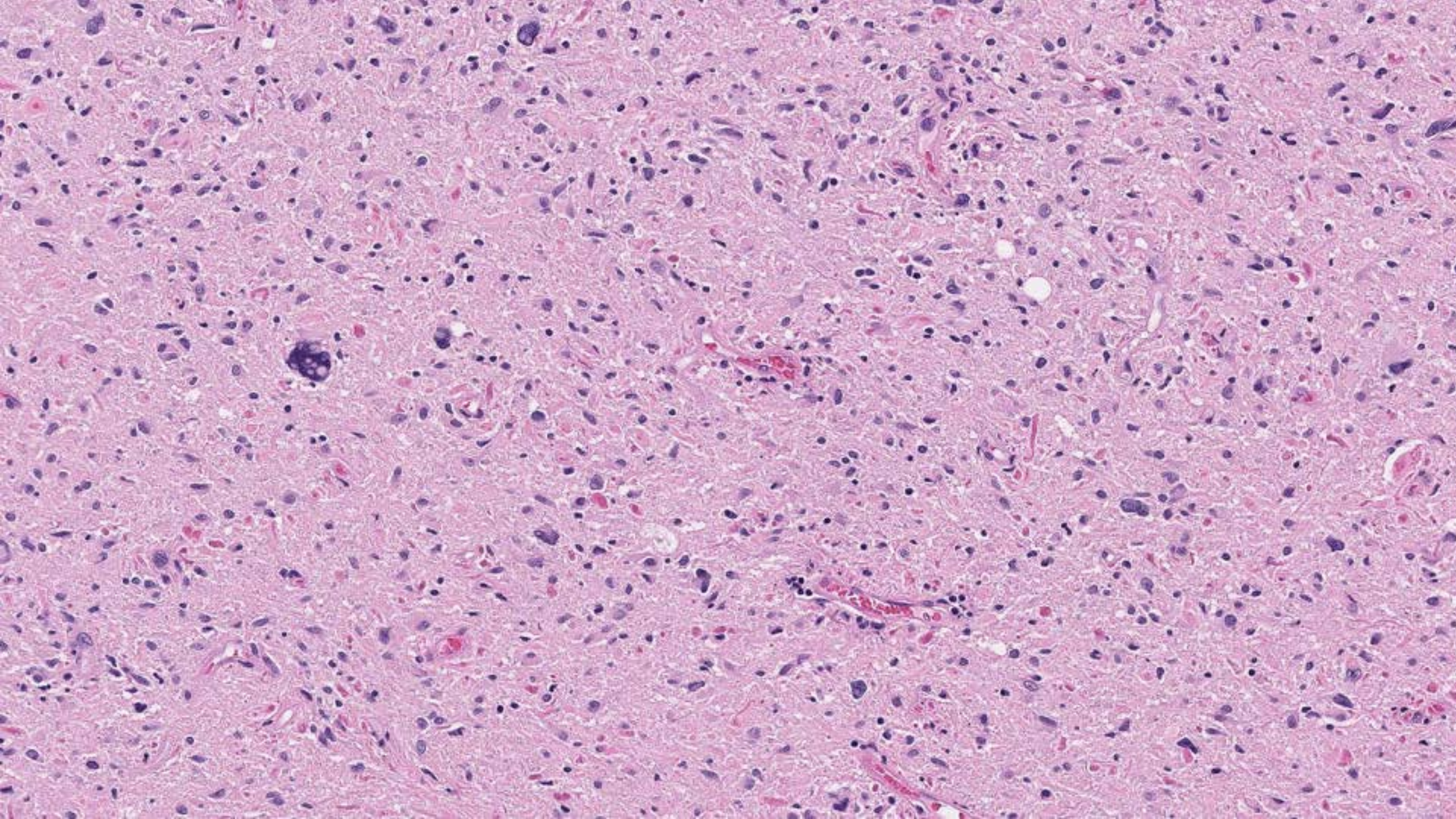
Fisher MJ et al. *Acta Neuropathol*. 2021.

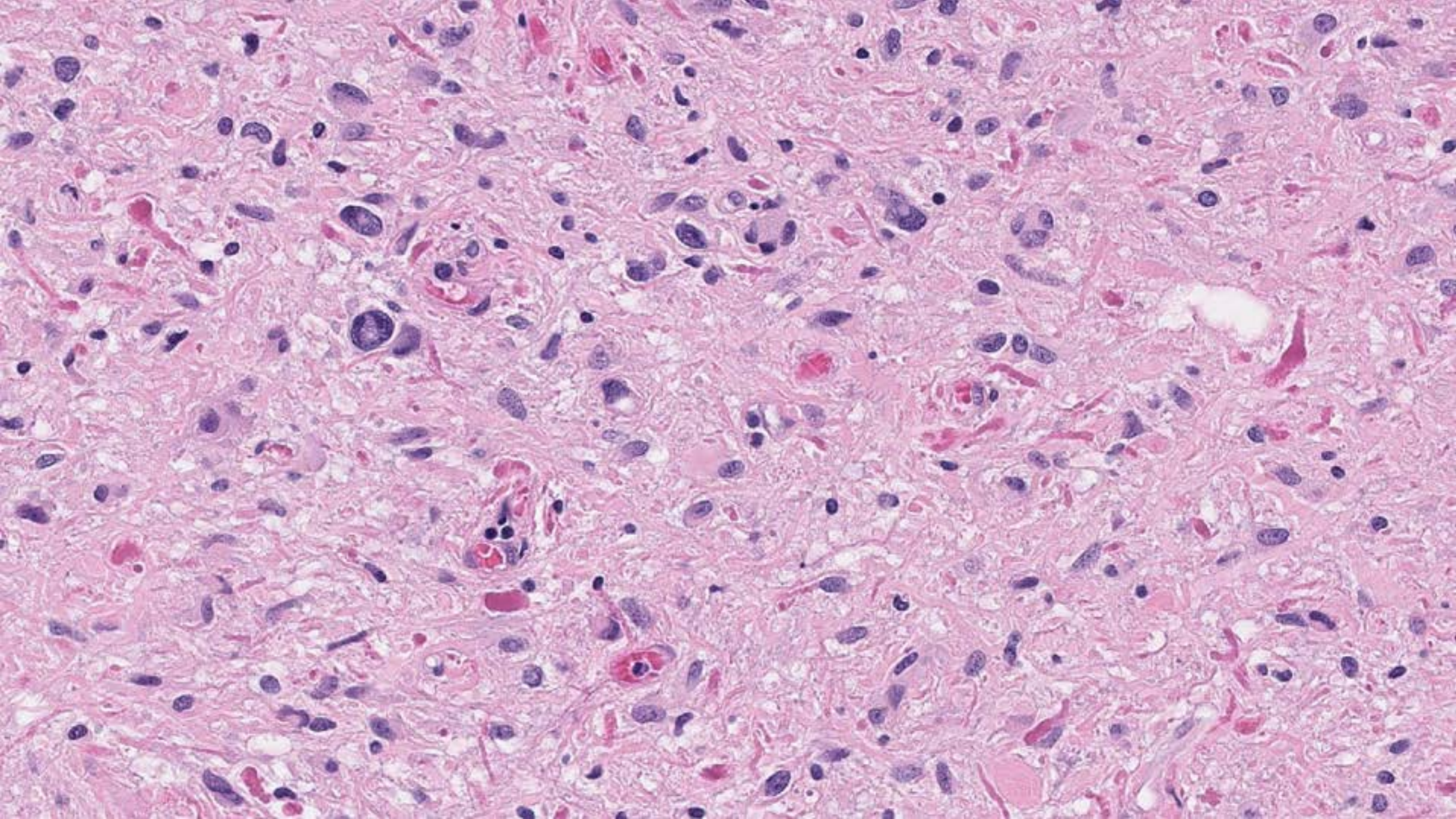


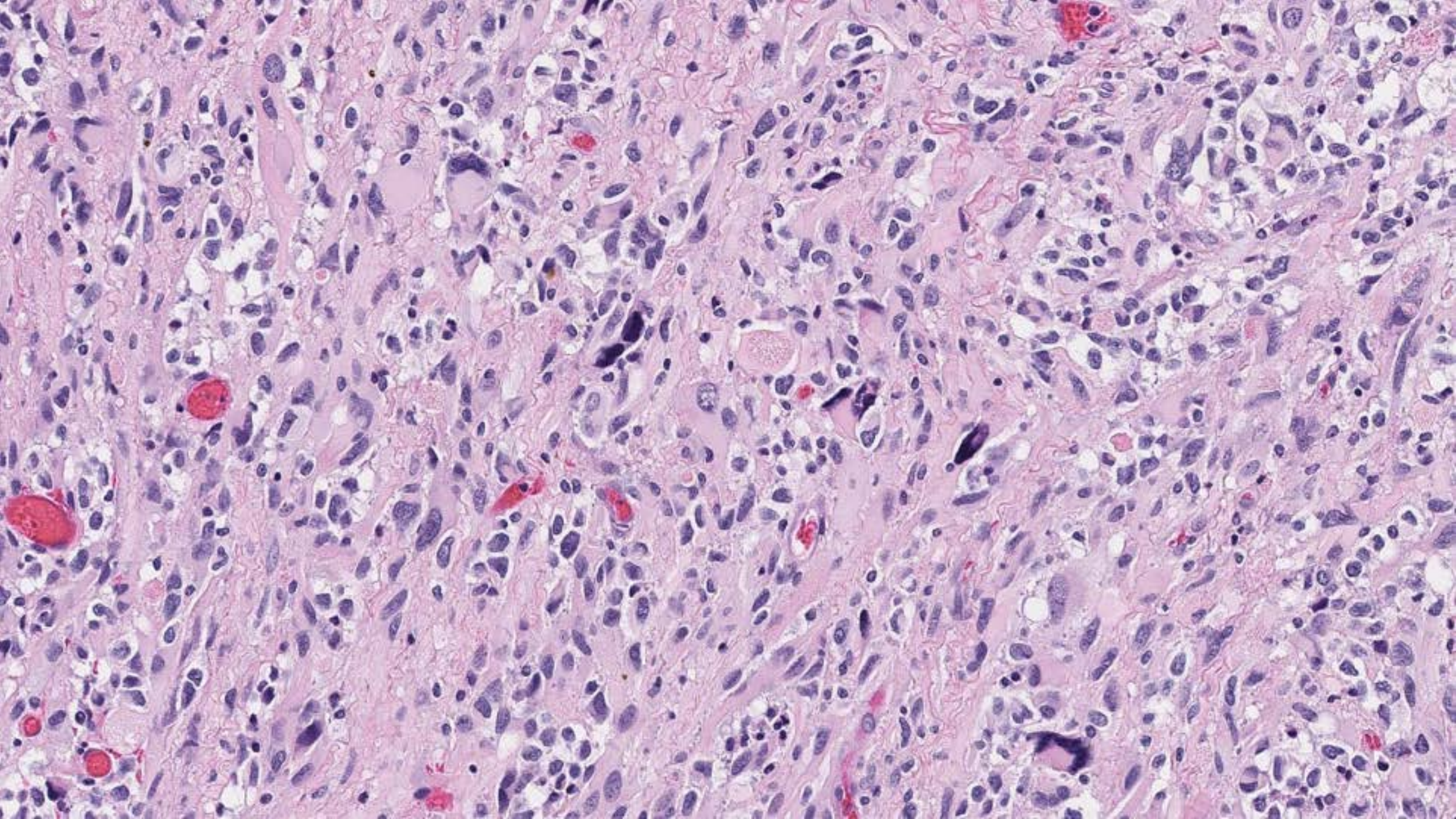
Case 1: Pilocytic astrocytoma

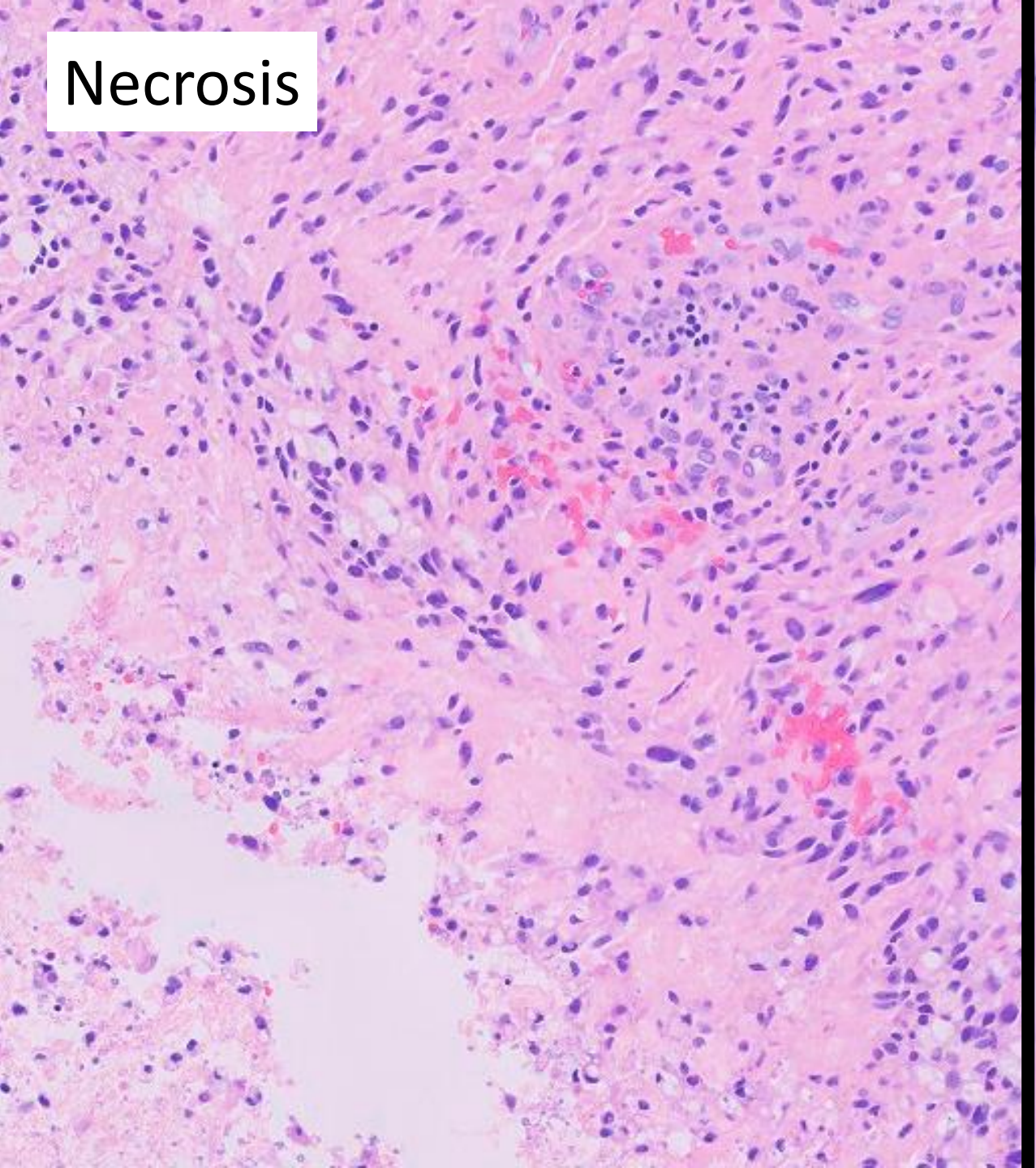
Case 2

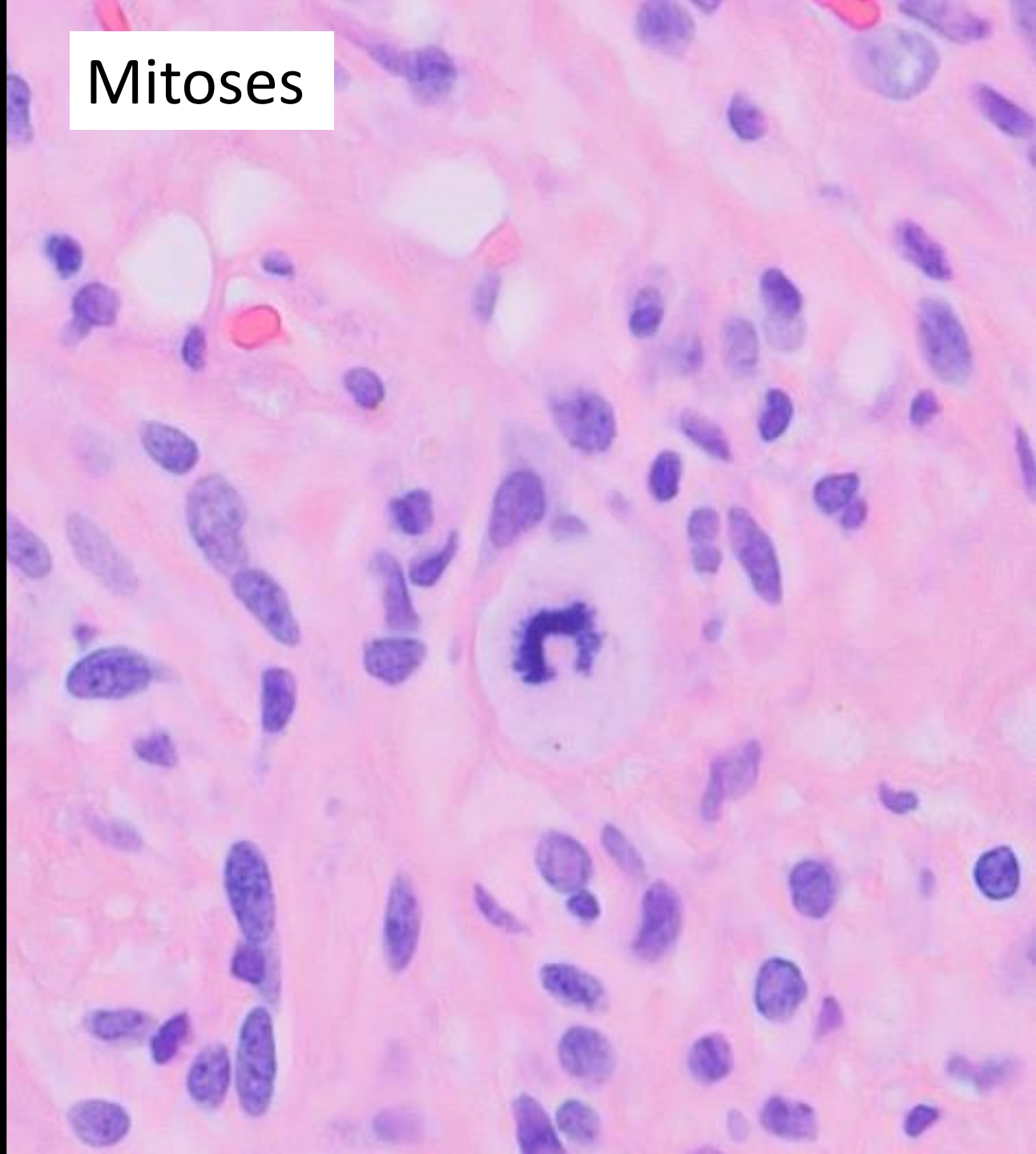
- 27-year-old woman with progressive headaches and gait instability
- Known history of NF1, prior excised cutaneous neurofibromas
- Heterogeneous mass with irregular enhancement centered within the left cerebellar hemisphere
- Undergoes resection (subtotal)

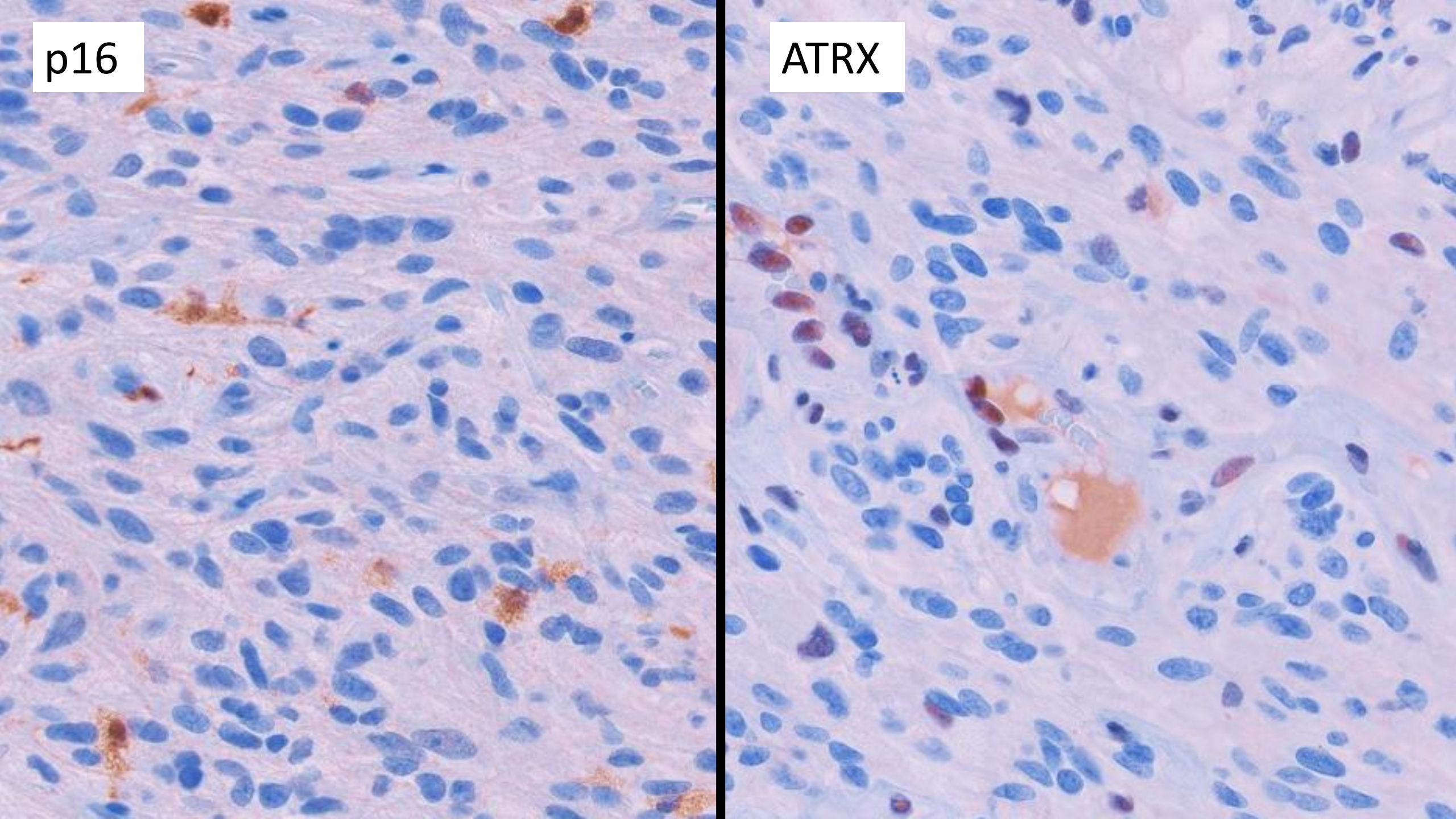




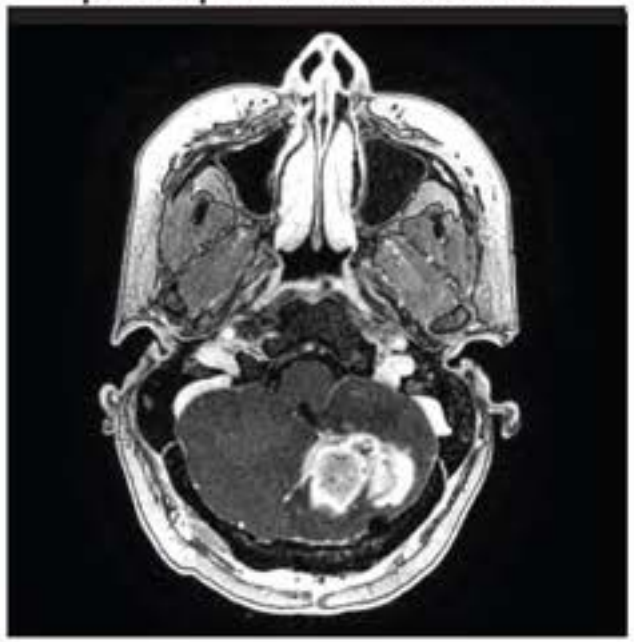



Necrosis

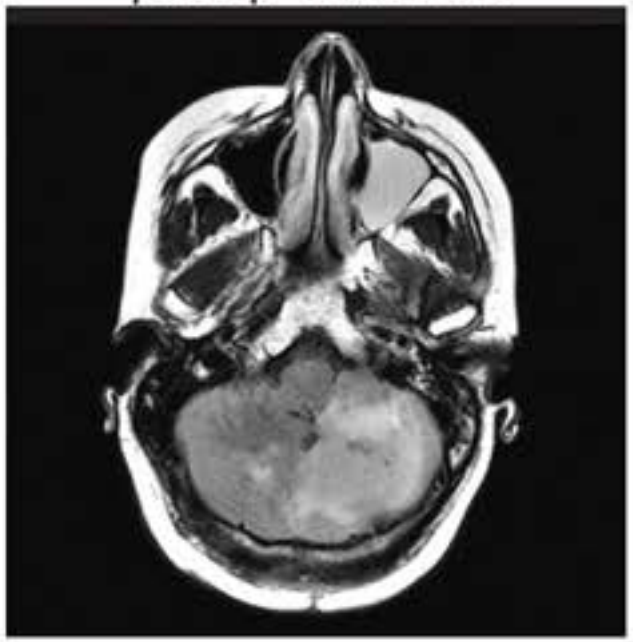

Mitoses

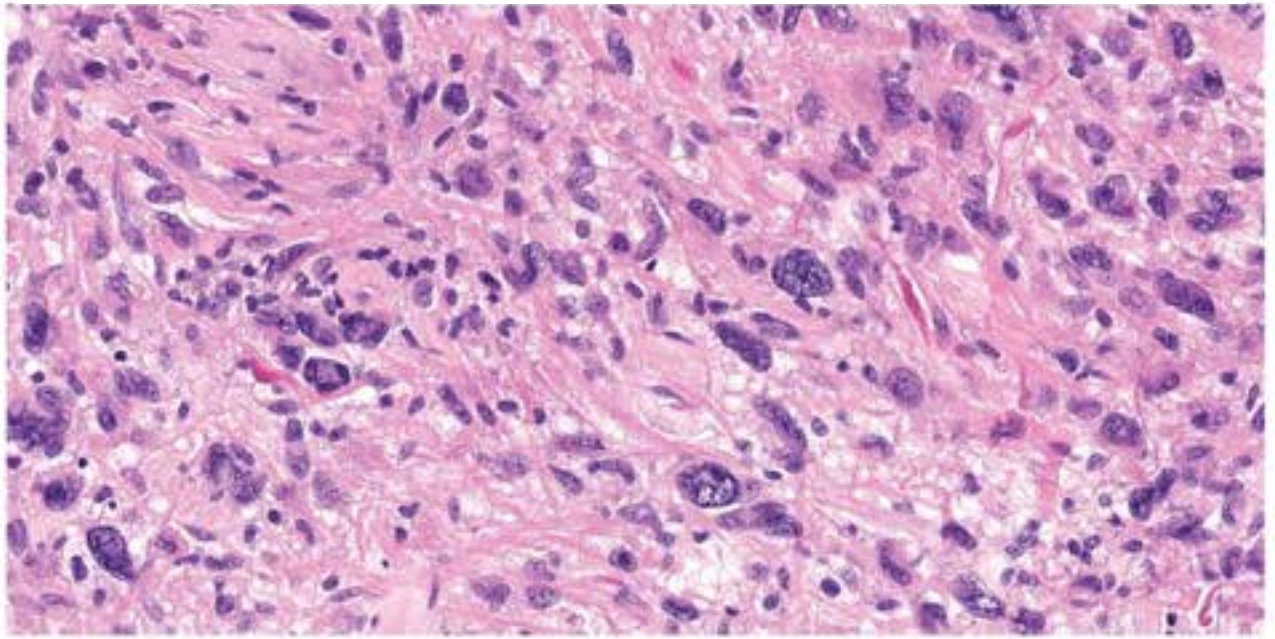

p16
ATRX

pre-op T1 w/ contrast



pre-op T2/FLAIR





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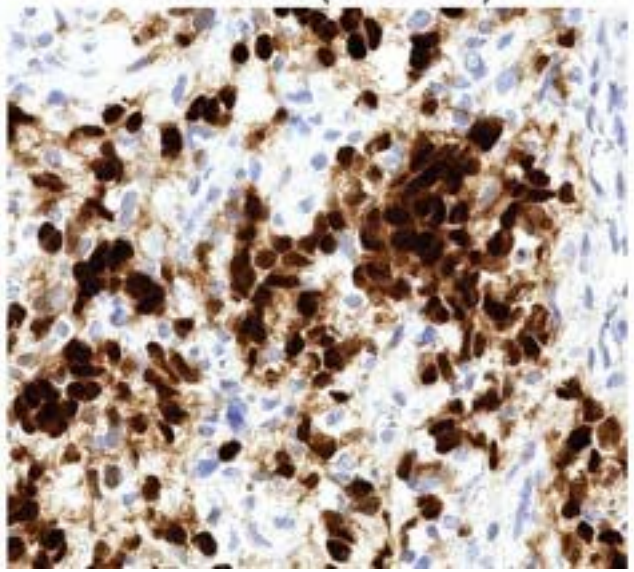
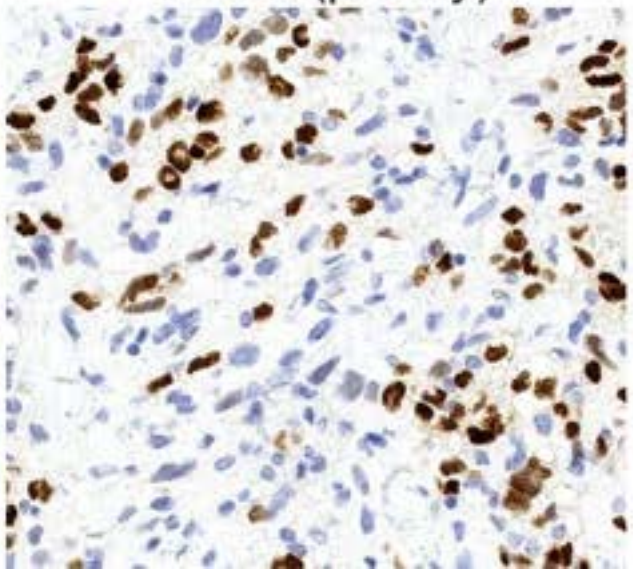
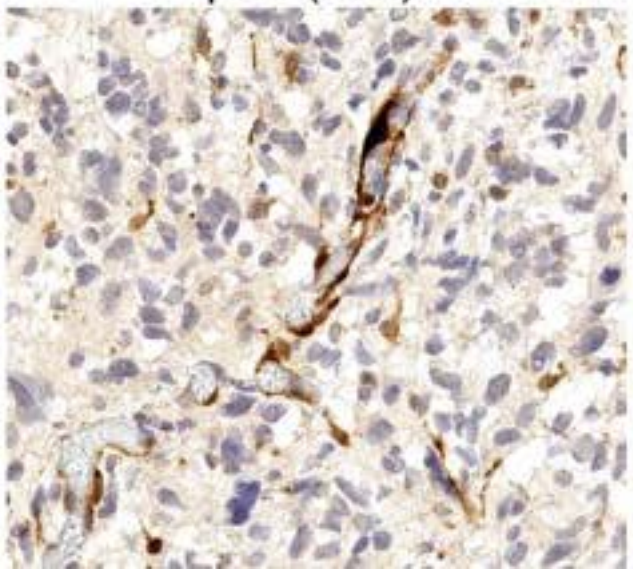


OLIG2 (patchy)



p16 (lost)



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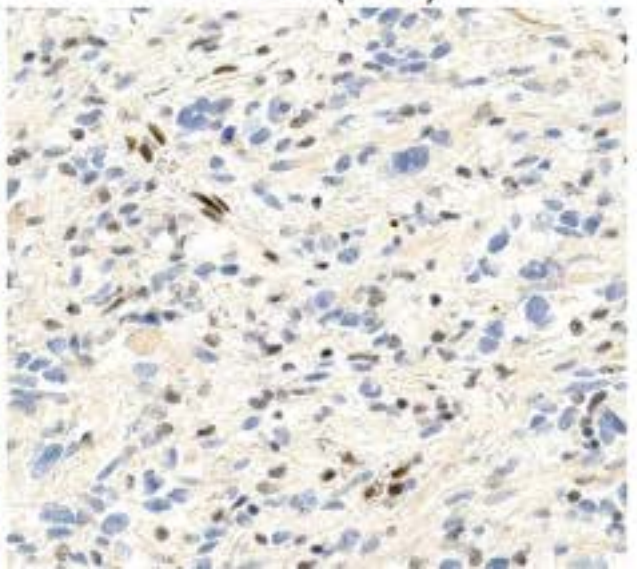

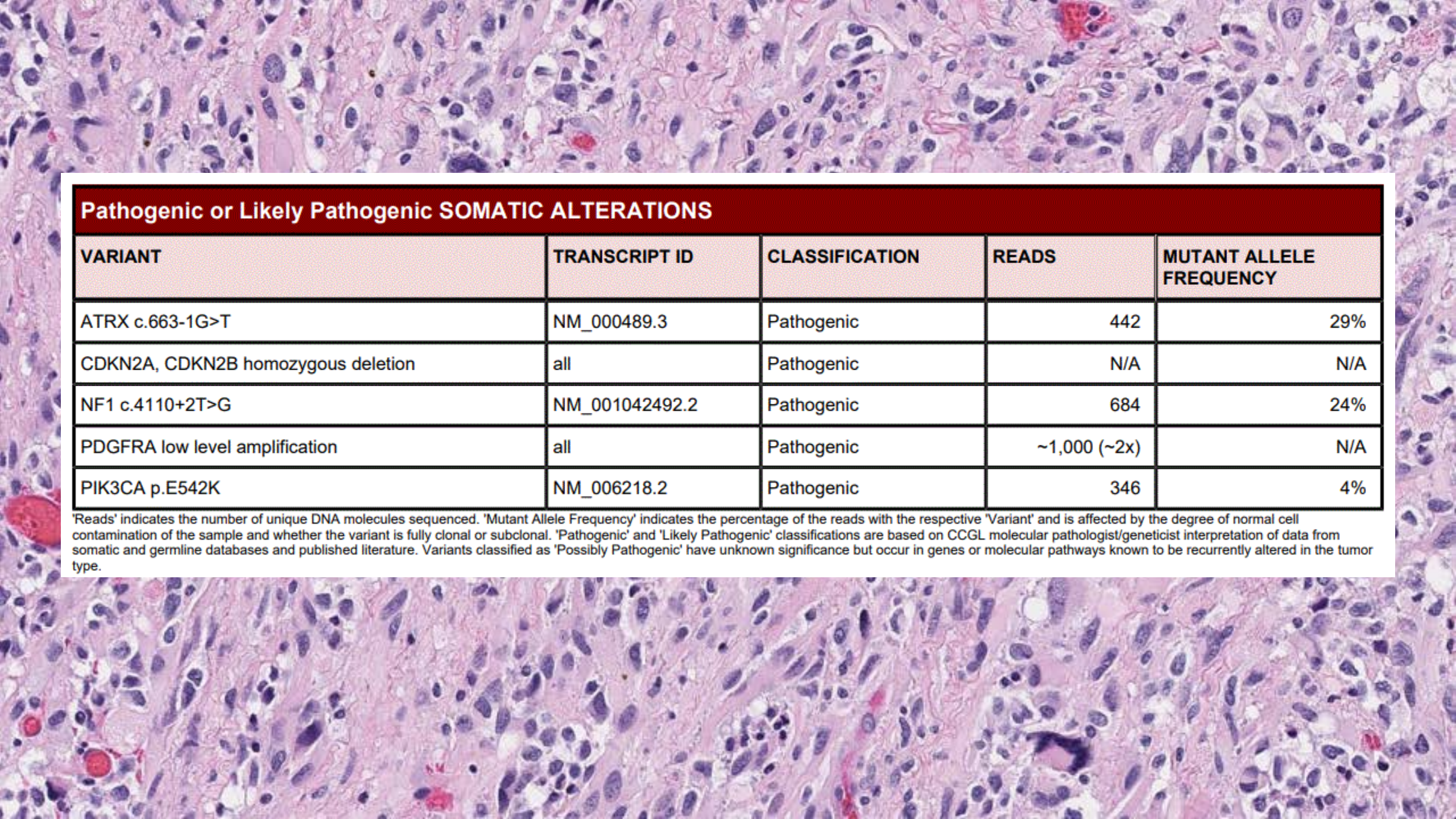

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
ATRX c.663-1G>T	NM_000489.3	Pathogenic	442	29%
CDKN2A, CDKN2B homozygous deletion	all	Pathogenic	N/A	N/A
NF1 c.4110+2T>G	NM_001042492.2	Pathogenic	684	24%
PDGFRA low level amplification	all	Pathogenic	~1,000 (~2x)	N/A
PIK3CA p.E542K	NM_006218.2	Pathogenic	346	4%

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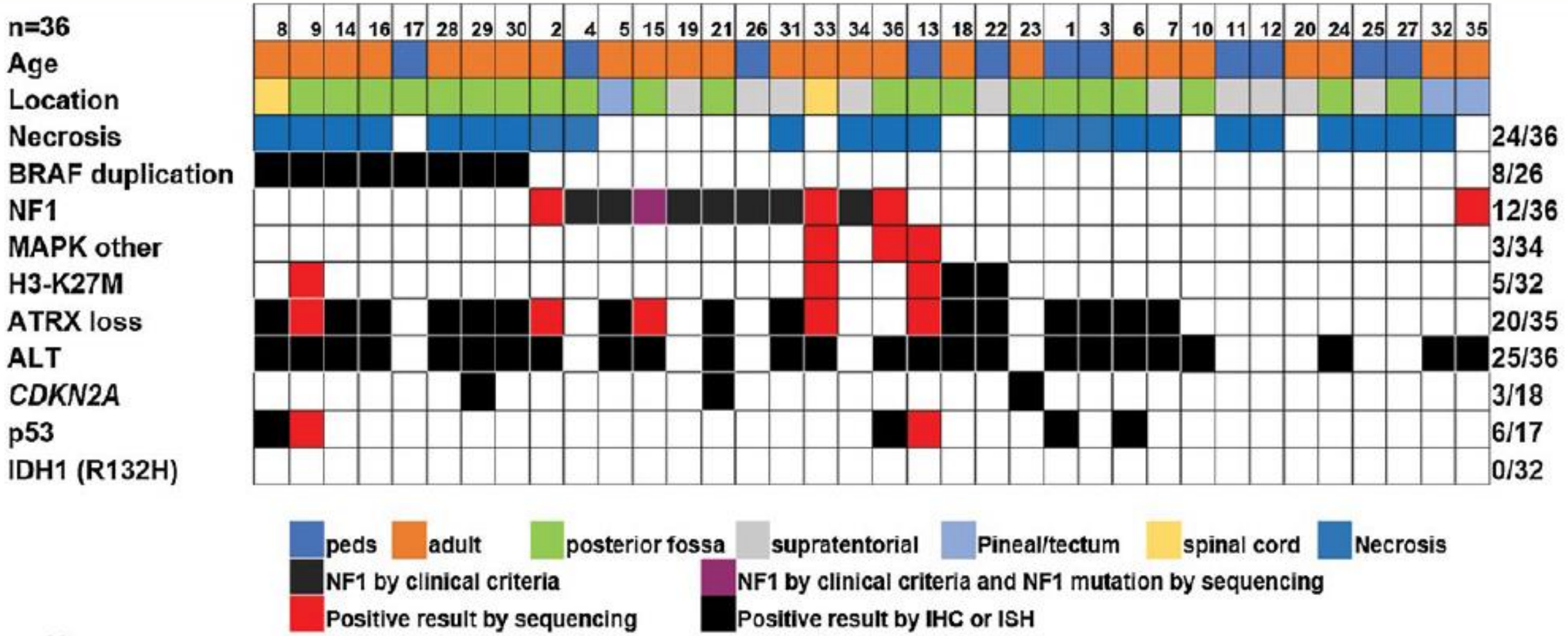
Alternative lengthening of telomeres, ATRX loss and H3-K27M mutations in histologically defined pilocytic astrocytoma with anaplasia



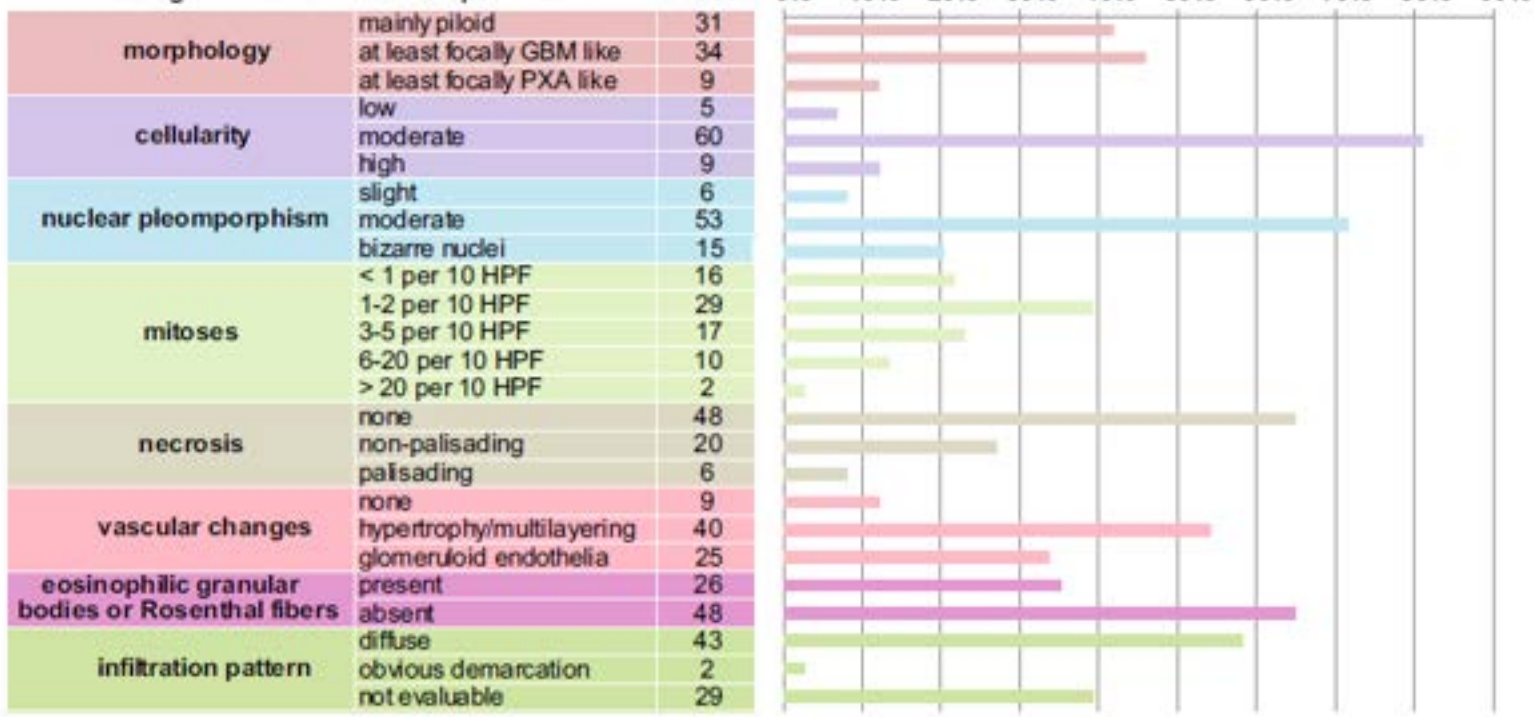
Rodriguez FJ et al. *Brain Pathol*. 2019.

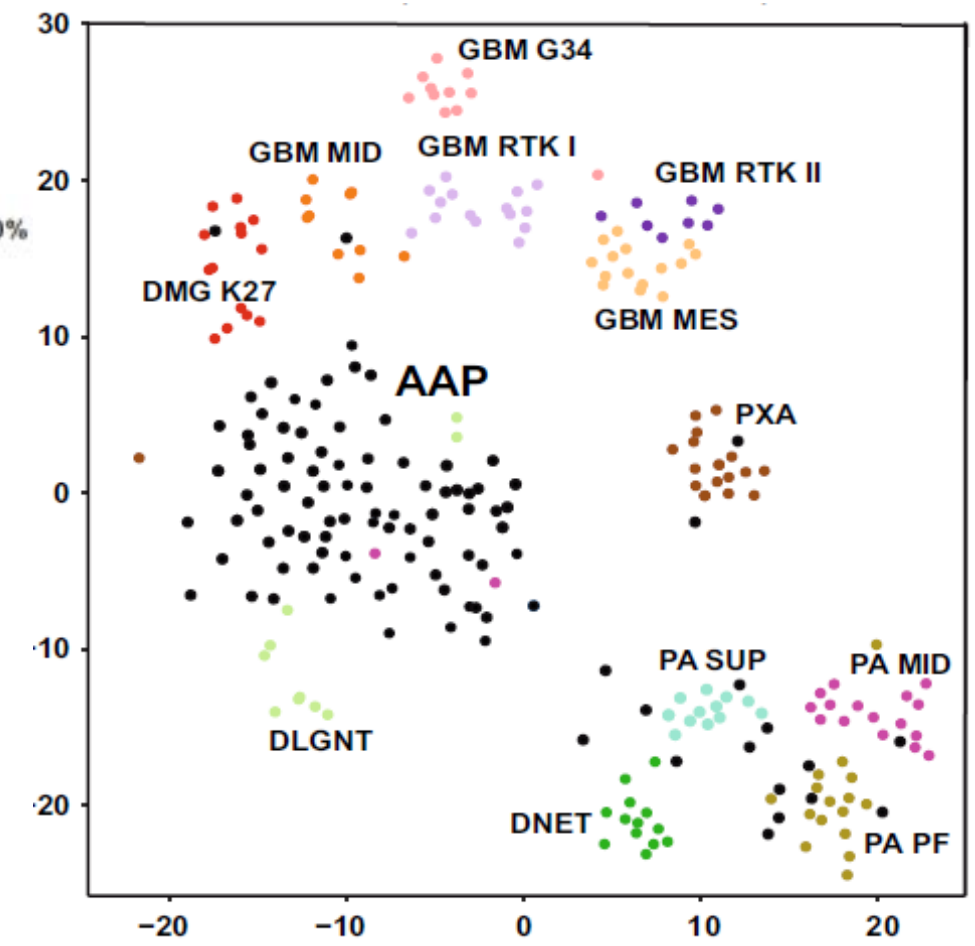
Acta Neuropathologica (2018) 136:273–291
https://doi.org/10.1007/s00401-018-1837-8

ORIGINAL PAPER

Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations

histological criterion	specification	# cases
morphology	mainly piloid	31
	at least focally GBM like	34
	at least focally PXA like	9
cellularity	low	5
	moderate	60
	high	9
nuclear pleomporphism	slight	6
	moderate	53
	bizarre nuclei	15
mitoses	< 1 per 10 HPF	16
	1-2 per 10 HPF	29
	3-5 per 10 HPF	17
	6-20 per 10 HPF	10
	> 20 per 10 HPF	2
necrosis	none	48
	non-palisading	20
	palisading	6
vascular changes	none	9
	hypertrophy/multilayering	40
	glomeruloid endothelia	25
eosinophilic granular bodies or Rosenthal fibers	present	26
	absent	48
infiltration pattern	diffuse	43
	obvious demarcation	2
	not evaluable	29





Reinhardt A et al. *Acta Neuropathol*. 2018.

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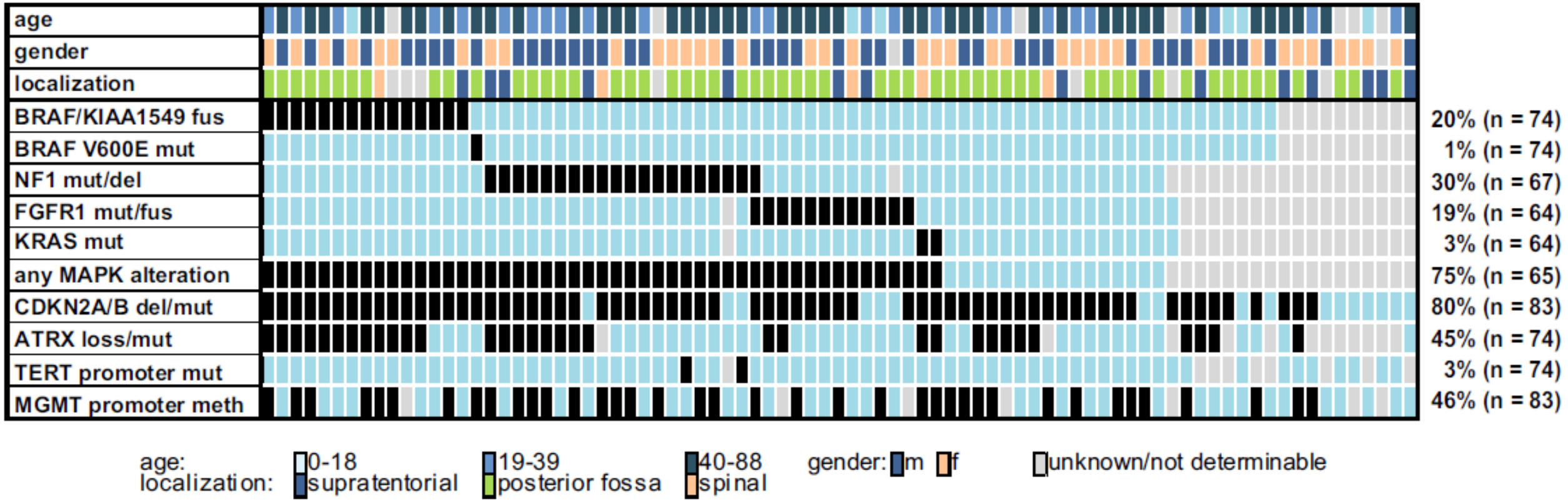

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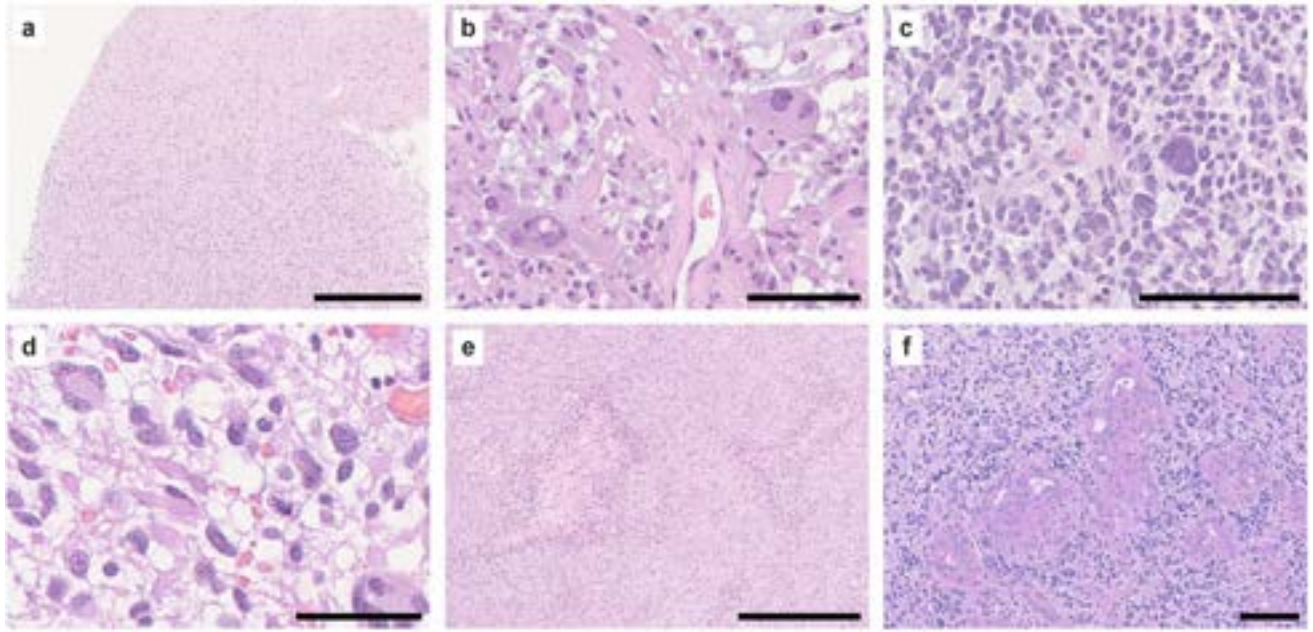
*methylation signature aligning with high confidence to “high-grade astrocytoma with piloid features” (HGAP)

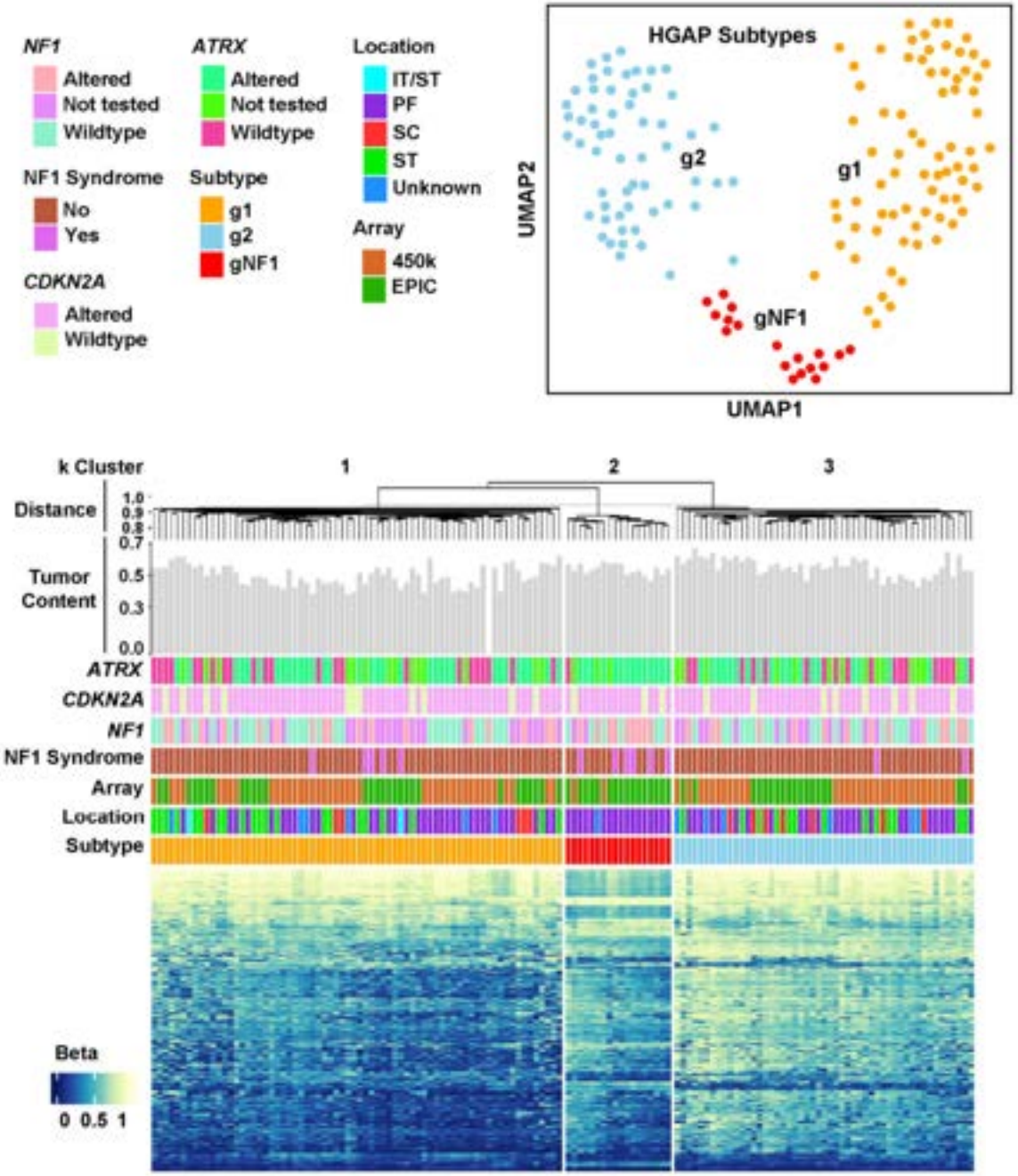
Acta Neuropathologica (2023) 145:71–82
https://doi.org/10.1007/s00401-022-02513-5

ORIGINAL PAPER

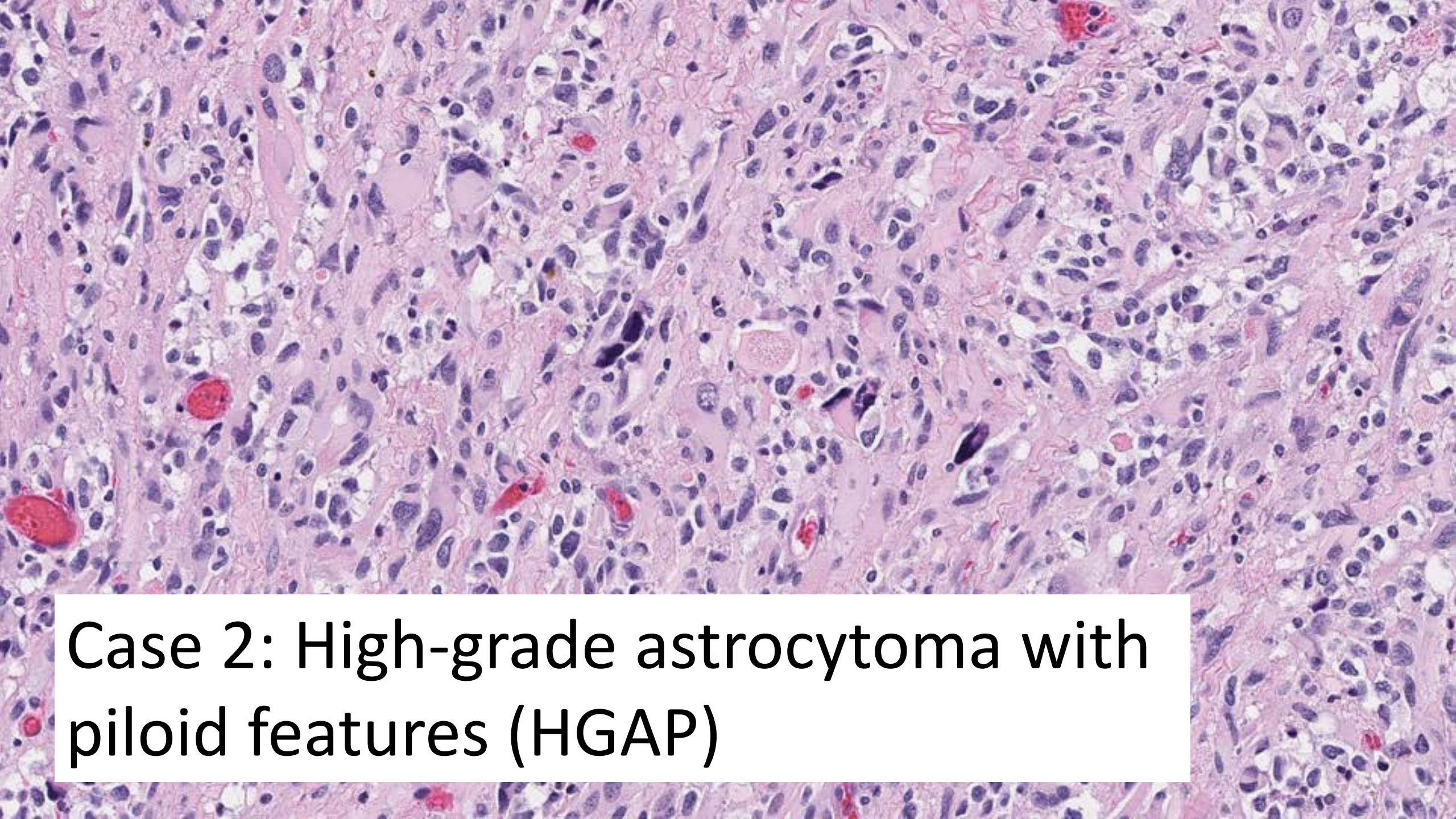
Expanded analysis of high-grade astrocytoma with piloid features identifies an epigenetically and clinically distinct subtype associated with neurofibromatosis type 1

Patrick J. Cimino[1] · Courtney Ketchum[2] · Rust Turakulov[2] · Omkar Singh[2] · Zied Abdullaev[2] · Caterina Giannini[3] · Peter Pytel[4] · Giselle Yvette Lopez[5] · Howard Colman[6] · MacLean P. Nasrallah[7] · Mariarita Santi[8] · Igor Lima Fernandes[9] · Jeff Nirschl[10] · Sonika Dahiya[11] · Stewart Neill[12] · David Solomon[13] · Eilis Perez[14] · David Capper[14] · Haresh Mani[15] · Dario Caccamo[16] · Matthew Ball[17] · Michael Badruddoja[18] · Rati Chkheidze[19] · Sandra Camelo-Piragua[20] · Joseph Fullmer[21] · Sanda Alexandrescu[22] · Gabrielle Yeaney[23] · Charles Eberhart[24] · Maria Martinez-Lage[25] · Jie Chen[26] · Leor Zach[27] · B. K. Kleinschmidt-DeMasters[28] · Marco Hefti[29] · Maria-Beatriz Lopes[30] · Nicholas Nuechterlein[31] · Craig Horbinski[32] · Fausto J. Rodriguez[33] · Martha Quezado[2] · Drew Pratt[2] · Kenneth Aldape[2]





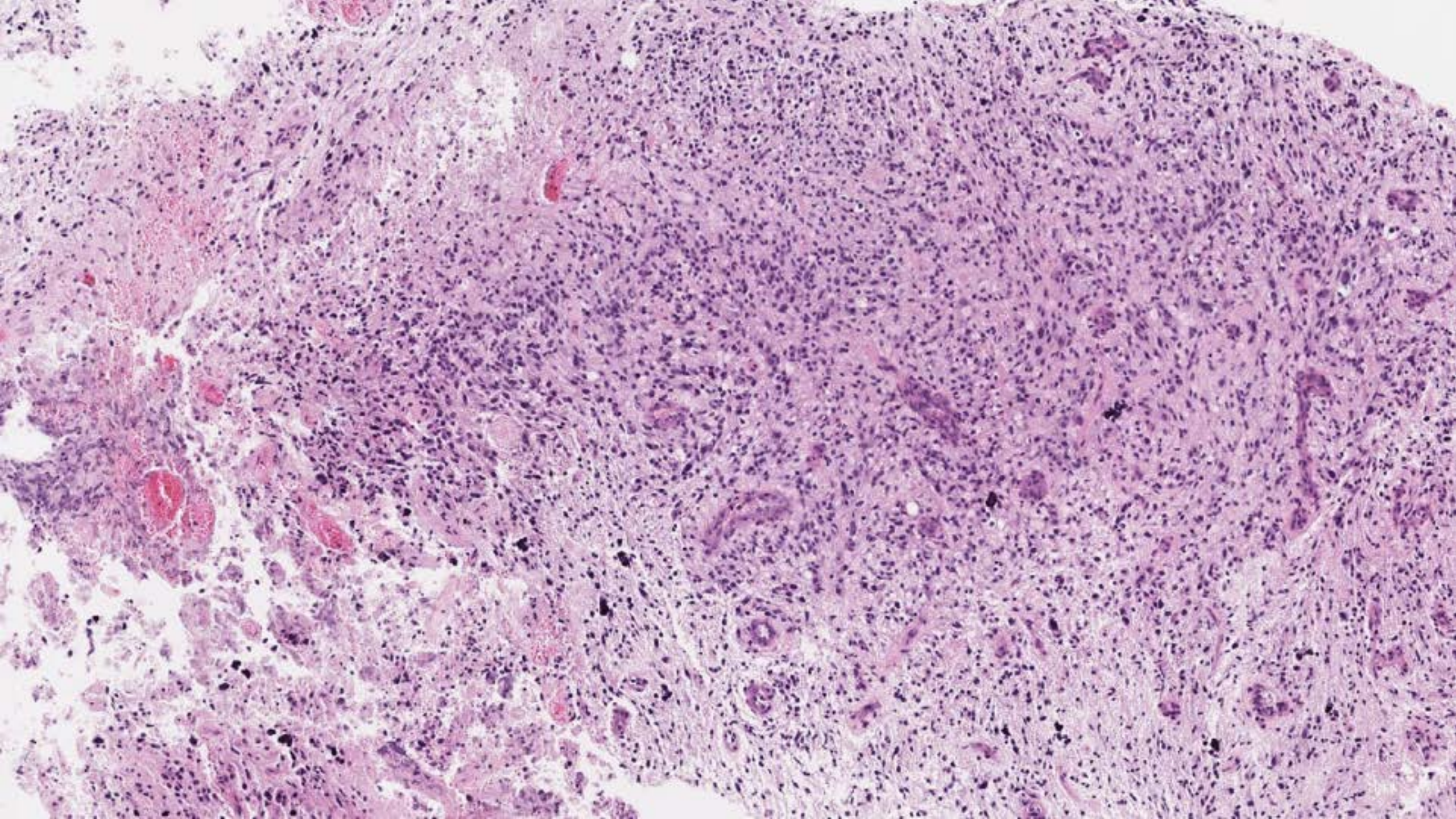
Cimino PJ et al. *Acta Neuropathol*. 2023.

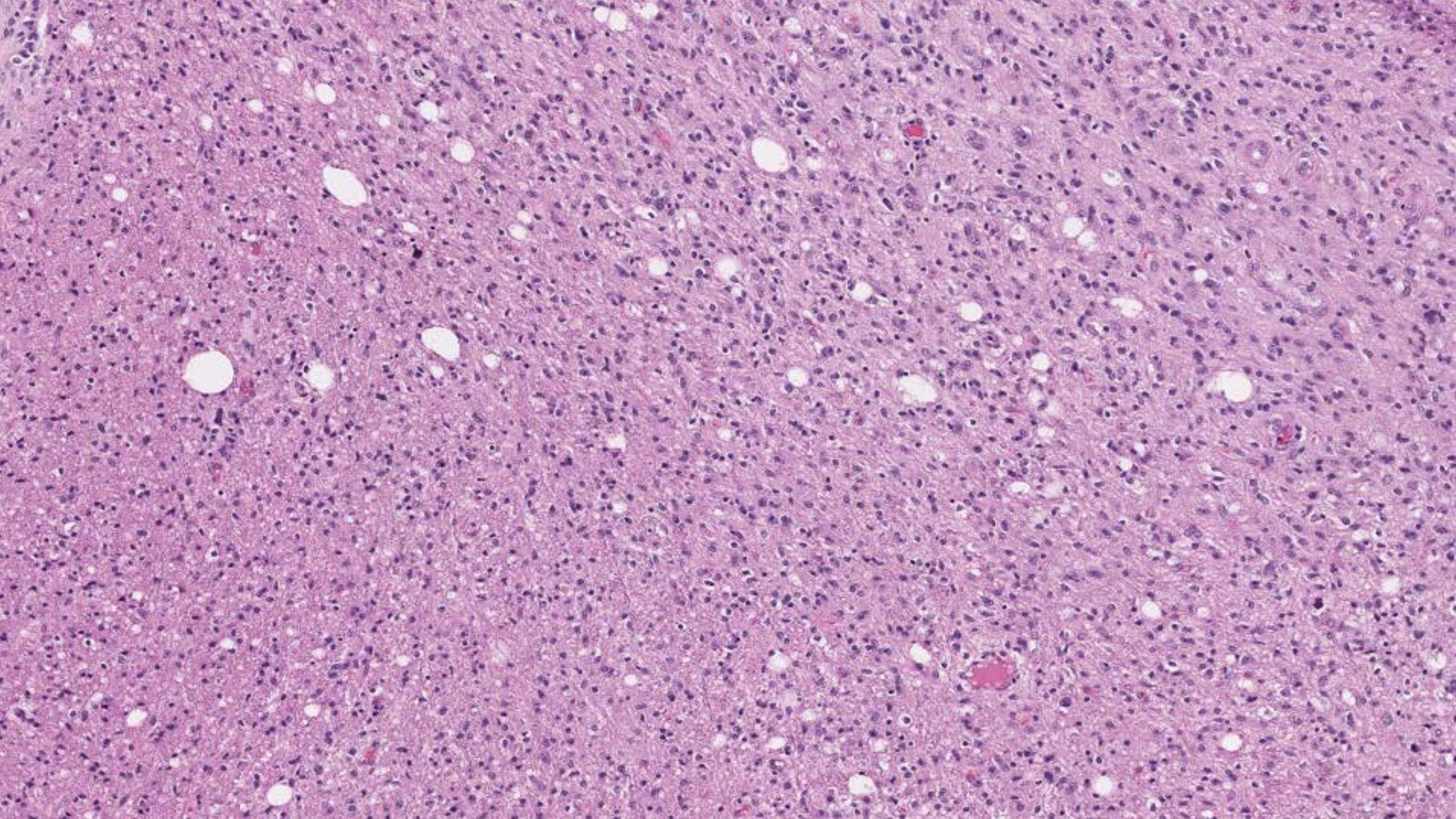


Case 2: High-grade astrocytoma with piloid features (HGAP)

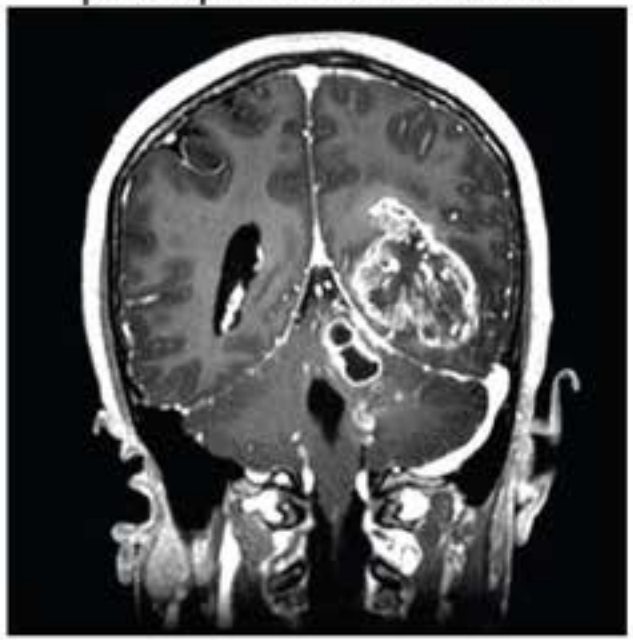
Case 3

- 40-year-old woman with new seizure
- Known history of NF1
- Heterogeneous mass centered in the left occipital lobe with irregular thick peripheral enhancement
- Undergoes resection

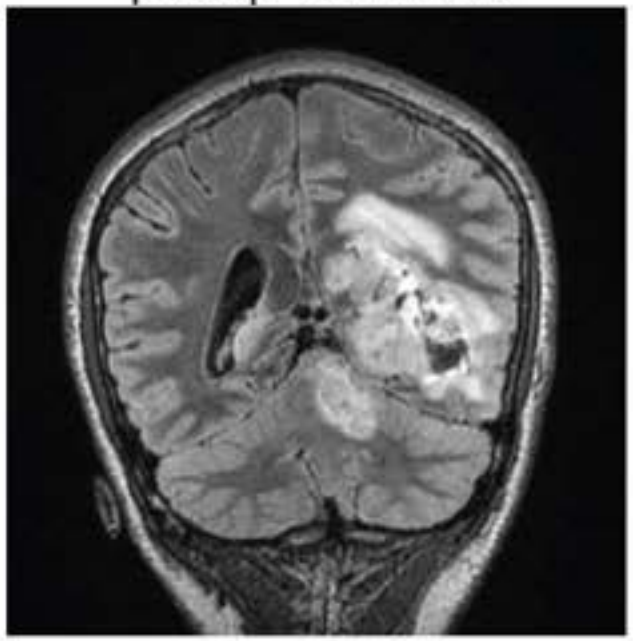


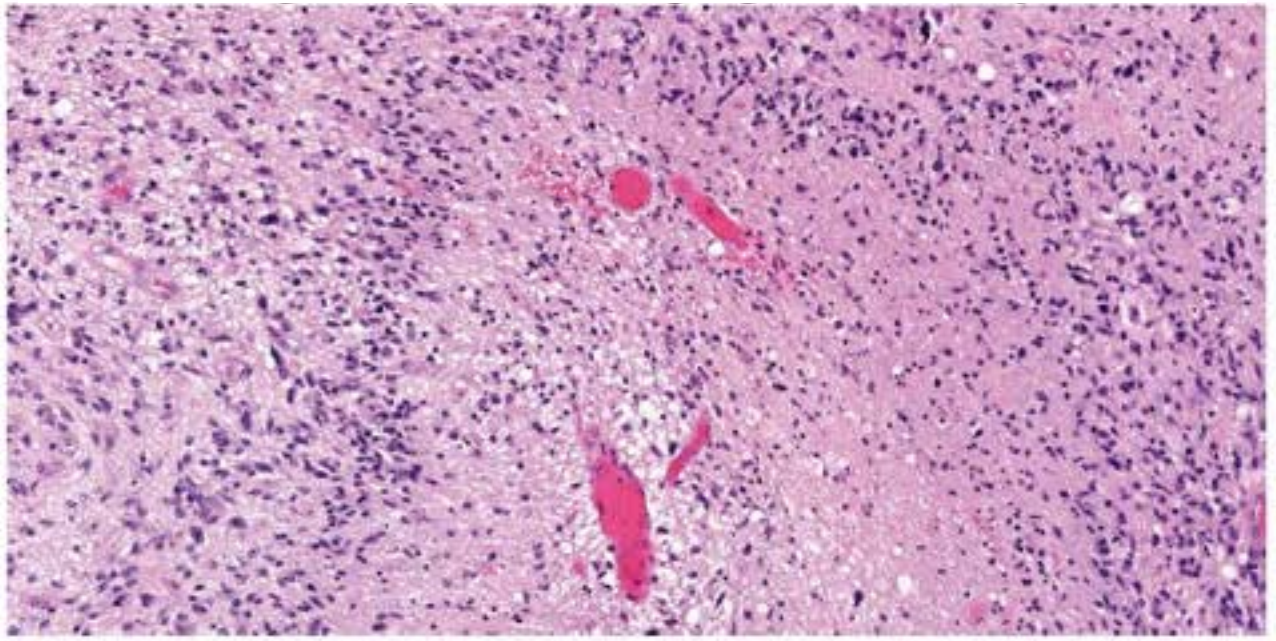


pre-op T1 w/ contrast

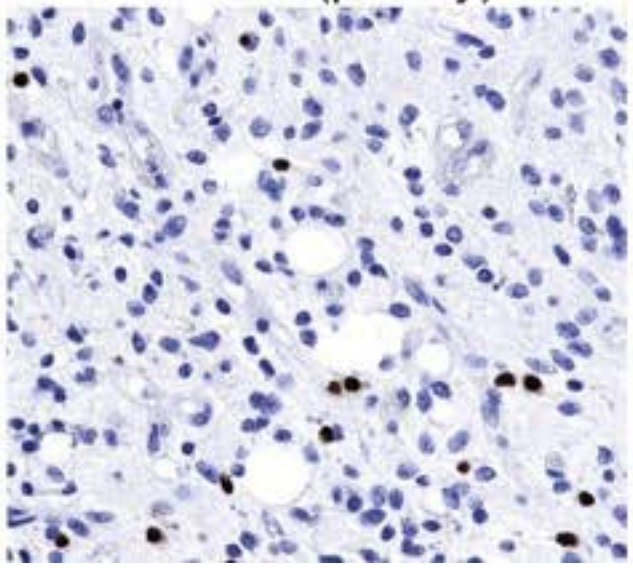


pre-op T2/FLAIR

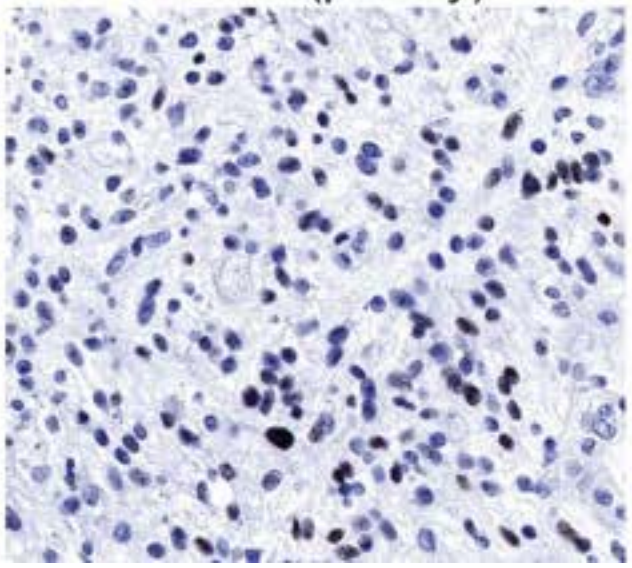




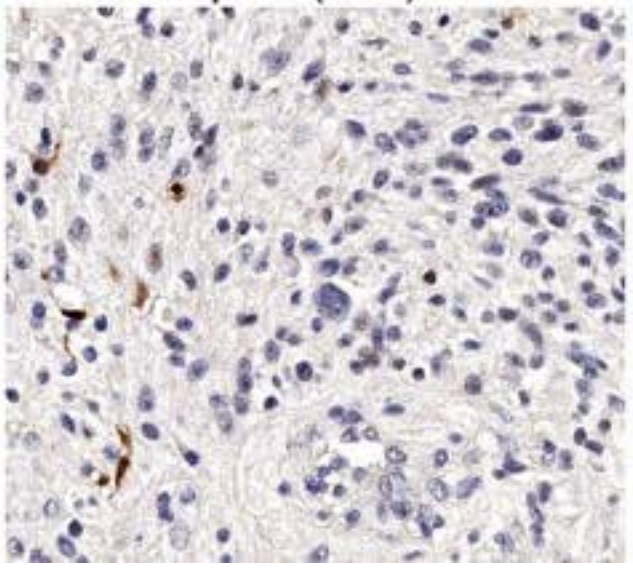
SOX10 (patchy)



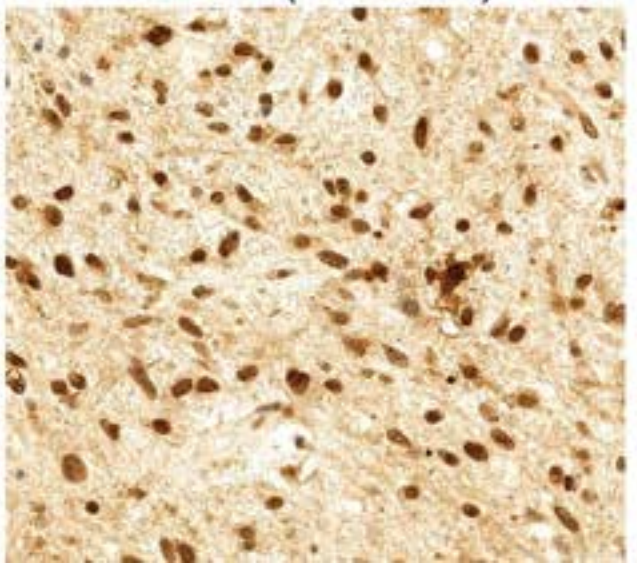
OLIG2 (patchy)

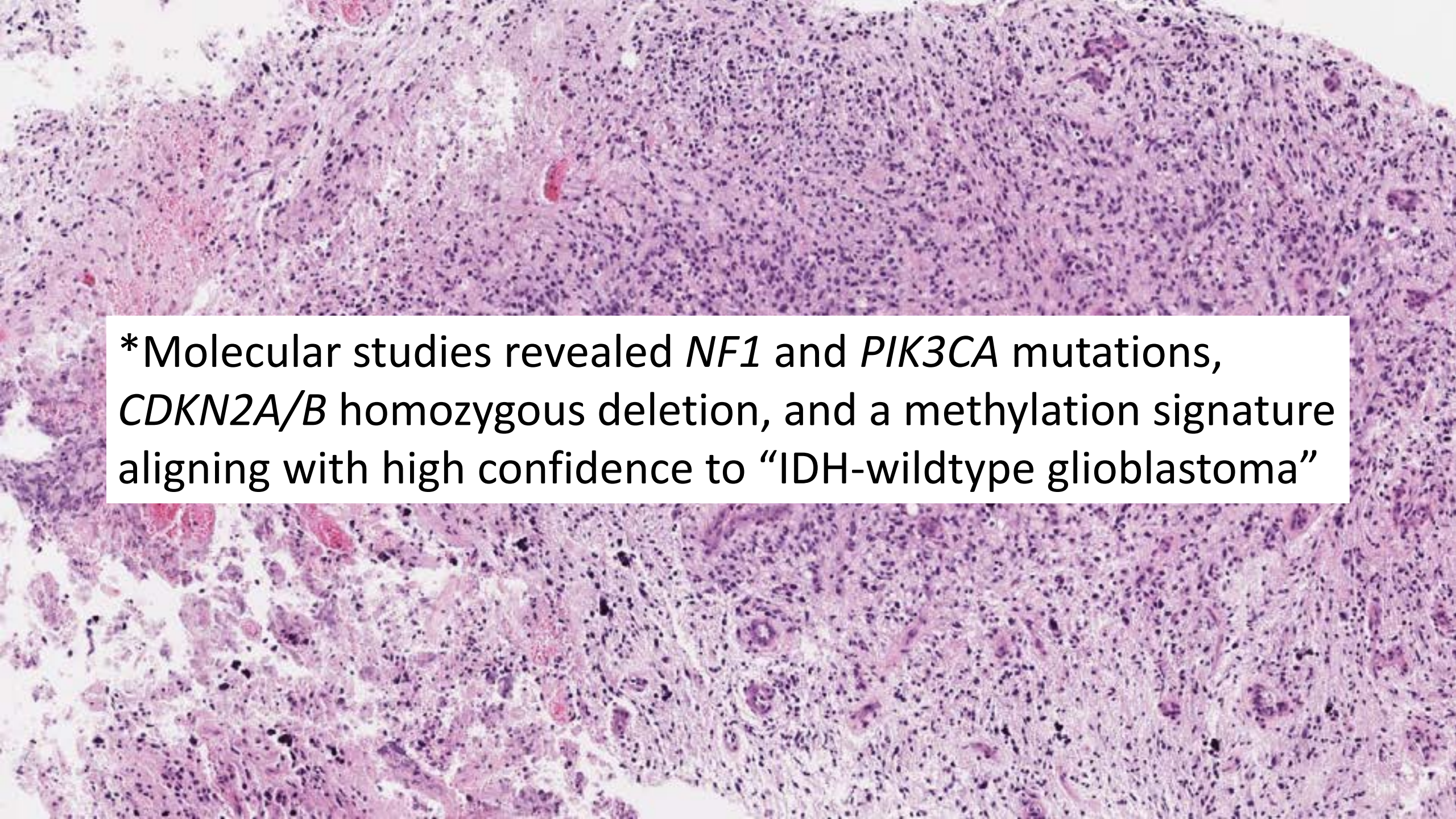


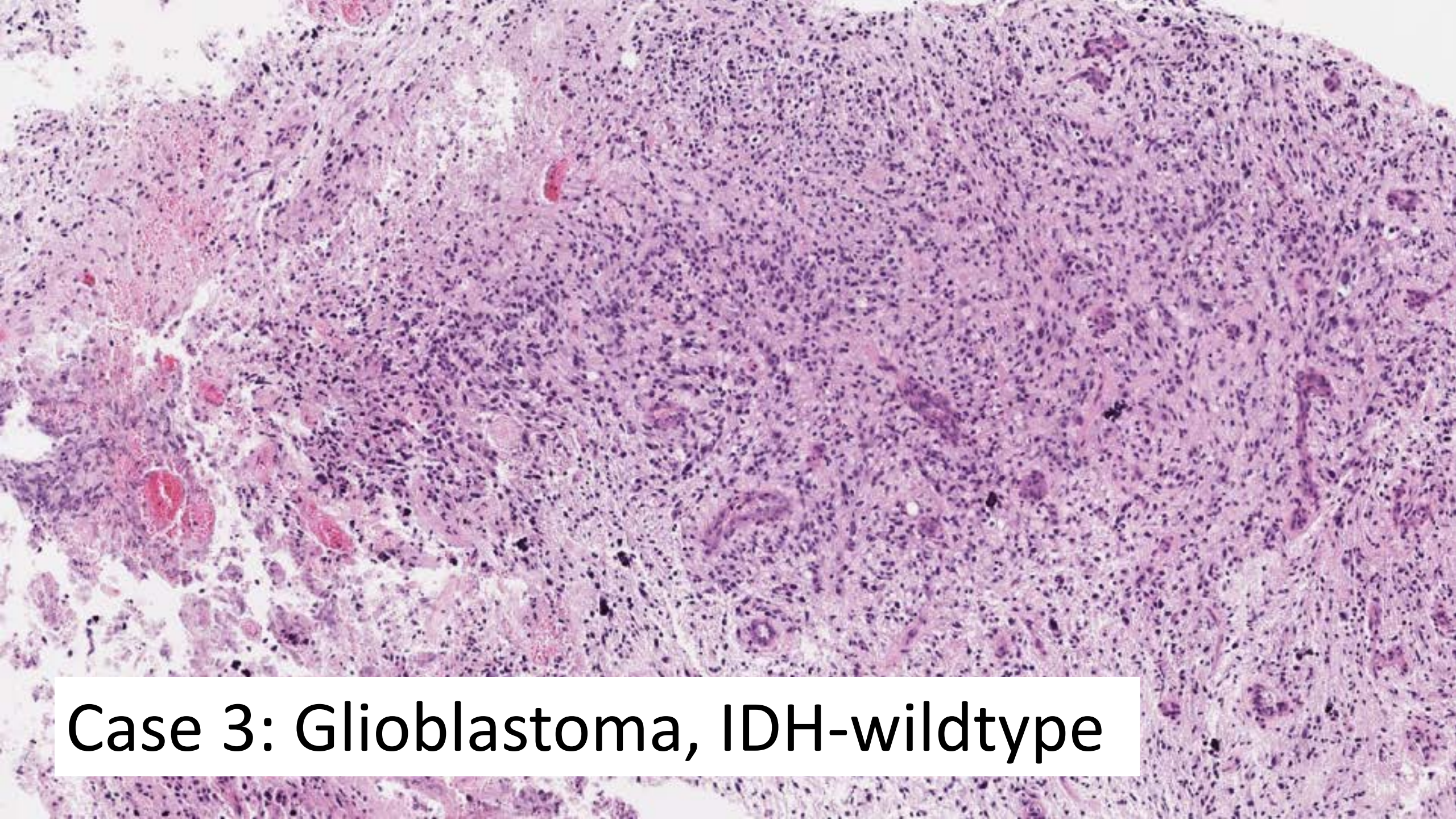
p16 (lost)



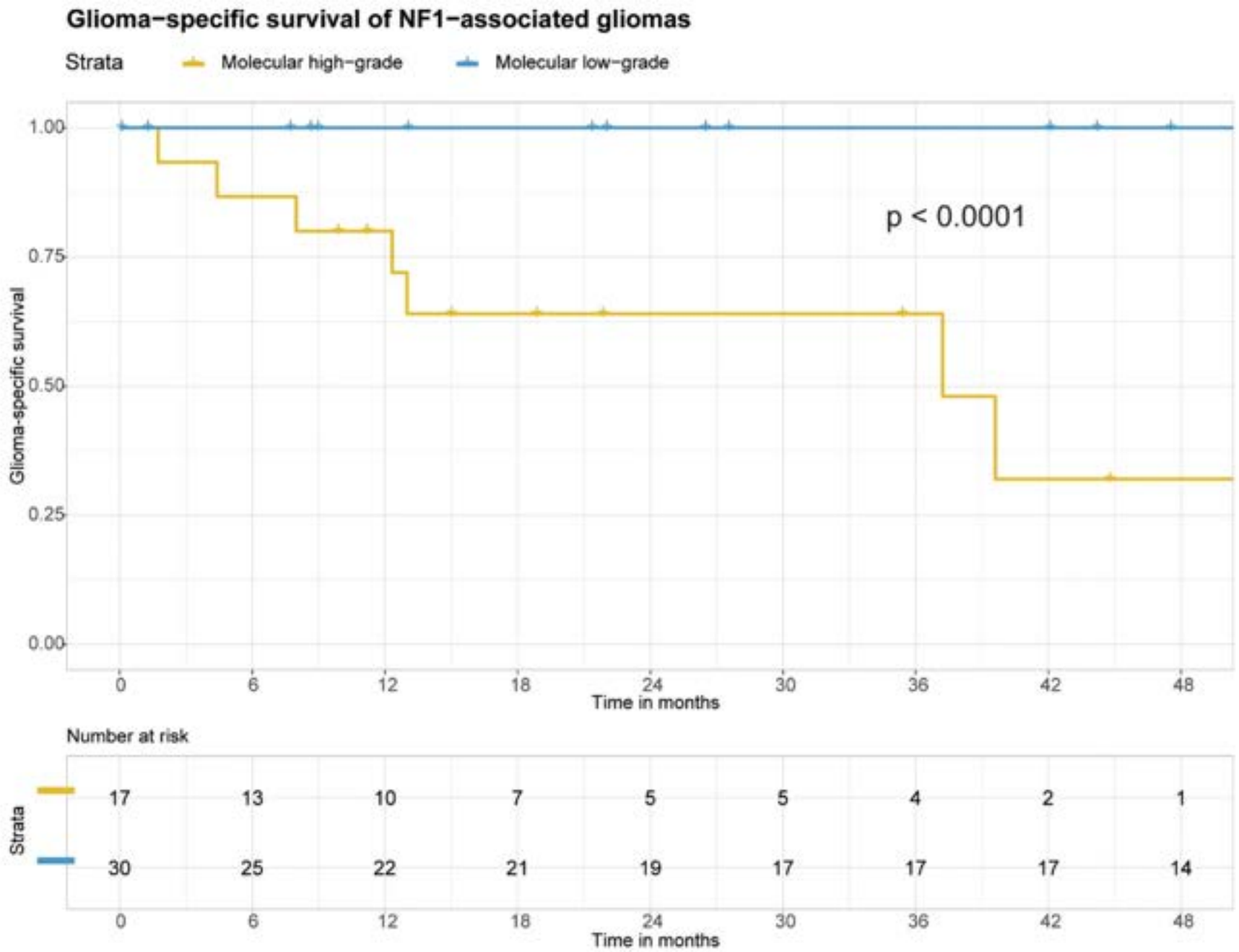
ATRX (retained)




*Molecular studies revealed *NF1* and *PIK3CA* mutations, *CDKN2A/B* homozygous deletion, and a methylation signature aligning with high confidence to “IDH-wildtype glioblastoma”



Case 3: Glioblastoma, IDH-wildtype

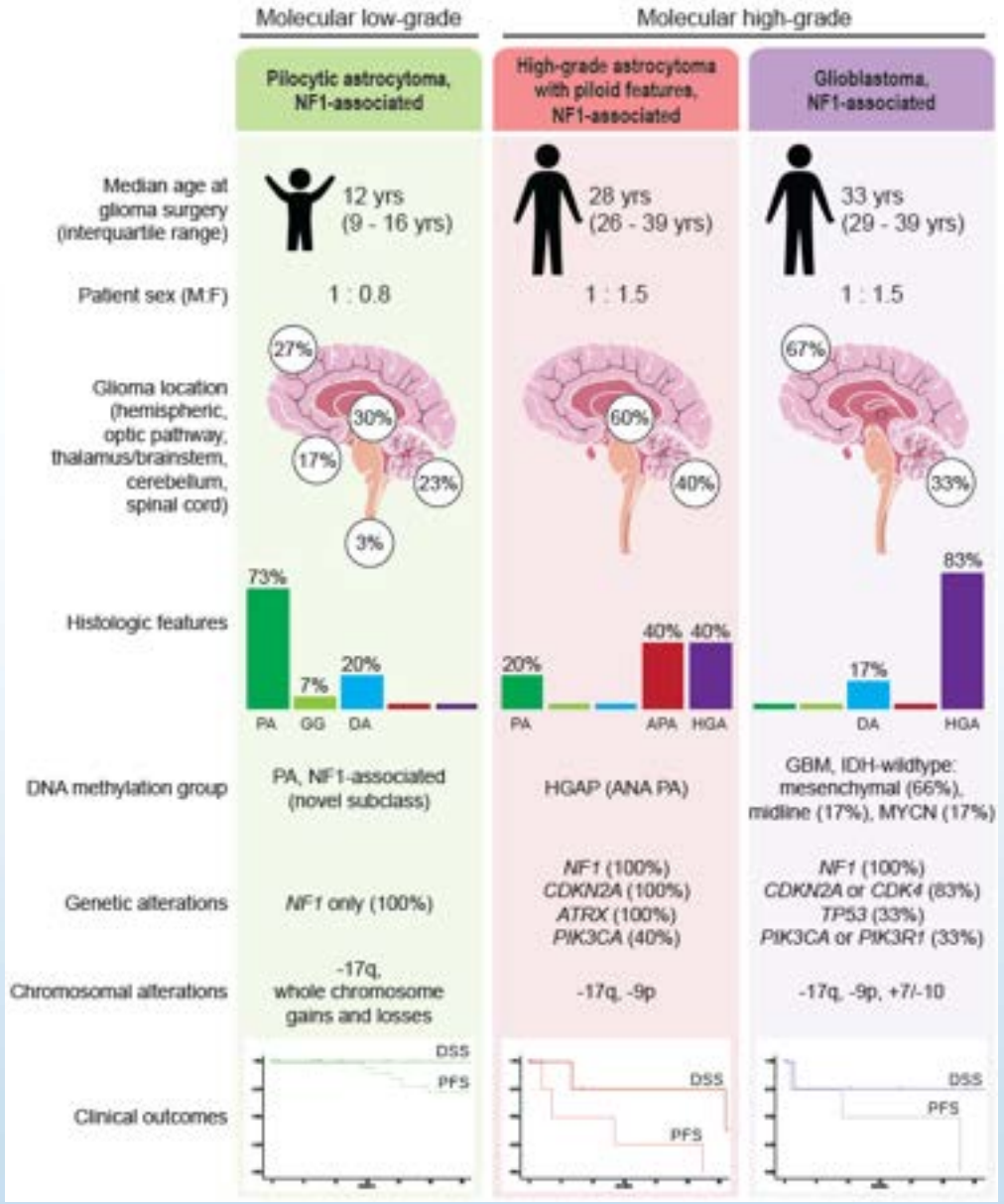


Lucas CG et al. *Acta Neuropathol*. 2022.

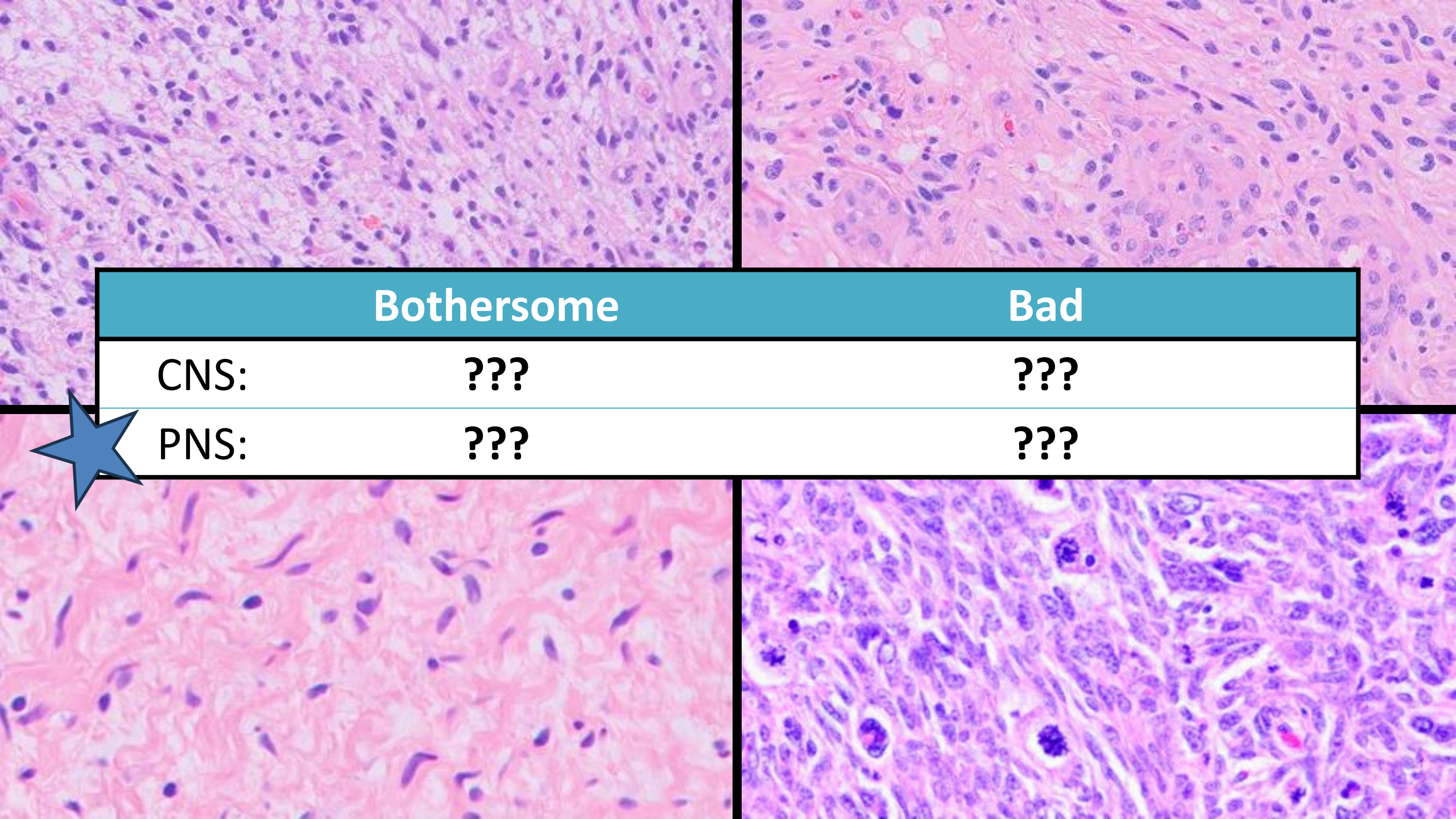
Gliomas arising in the setting of NF1 are heterogeneous

- Molecular low-grade
  - Younger patients
  - *NF1* biallelic inactivation only
    (+/- other MAPK alterations)
  - More favorable clinical outcomes
  - me3 group = pilocytic astrocytoma

- Molecular high-grade
  - Older patients
  - NF1 + add'l
    (*ATRX*, *CDKN2A*, *TP53*)
  - Less favorable clinical outcomes
  - Heterogeneous me3 groups



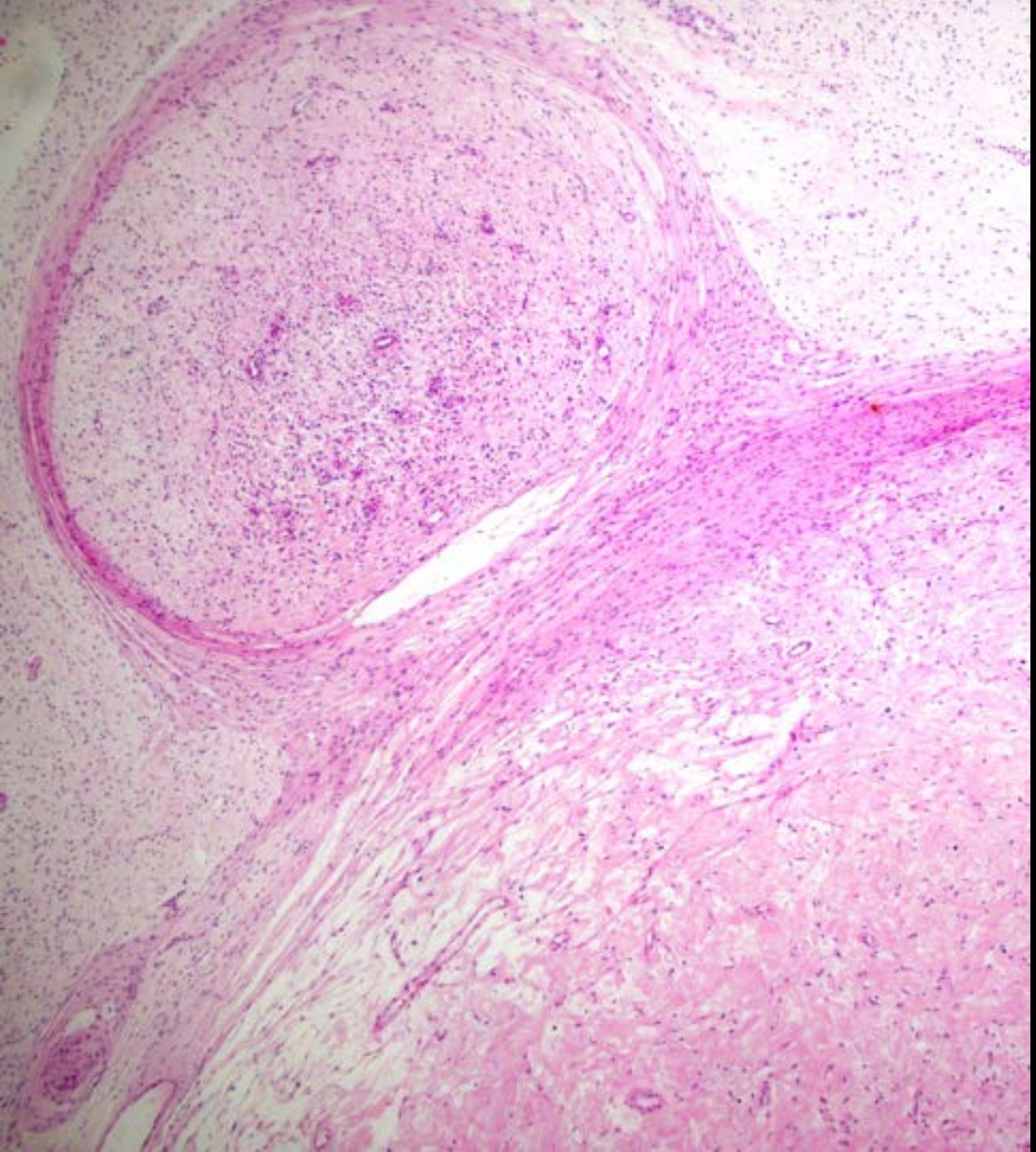
Lucas CG et al. *Acta Neuropathol*. 2022.

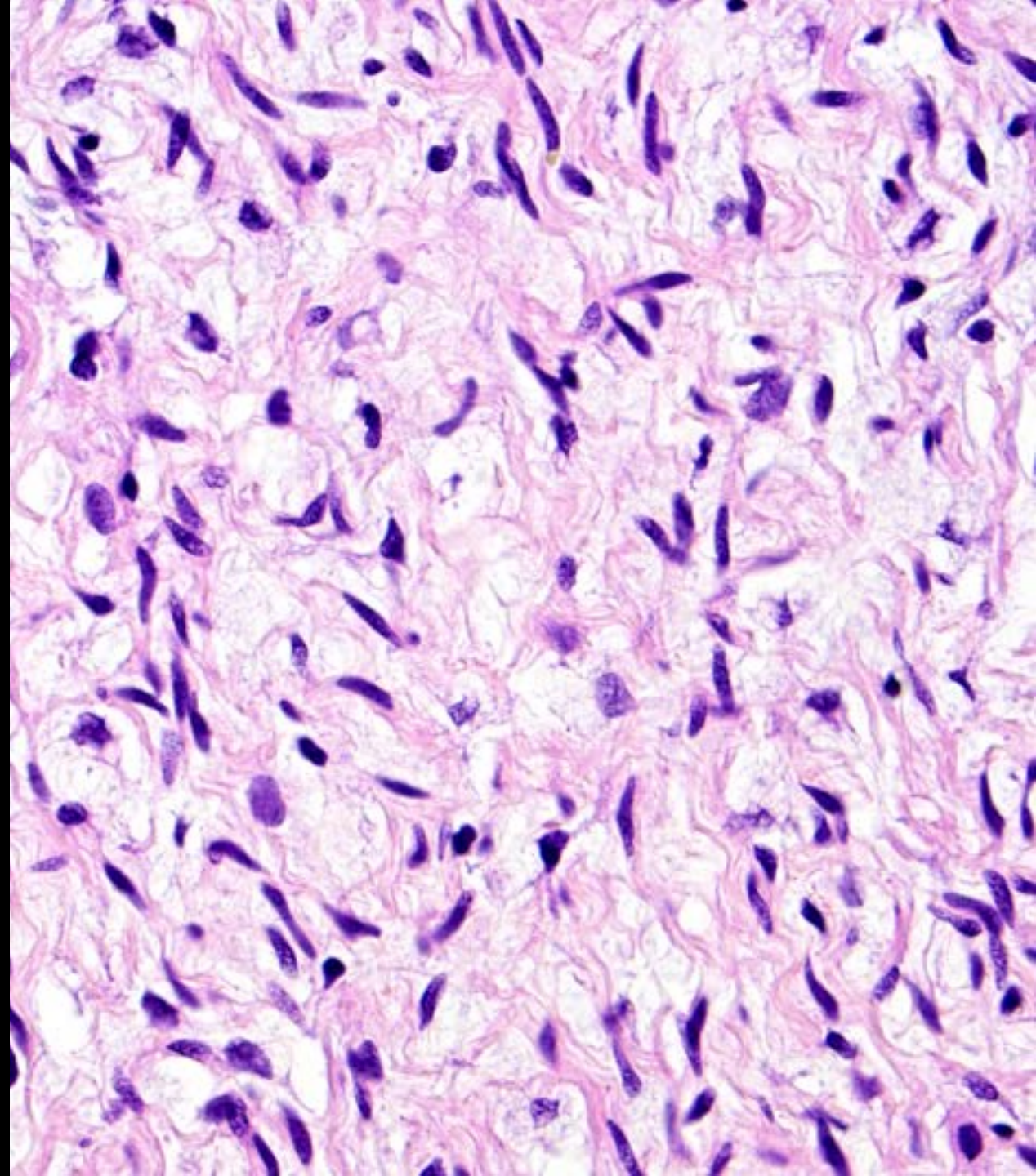


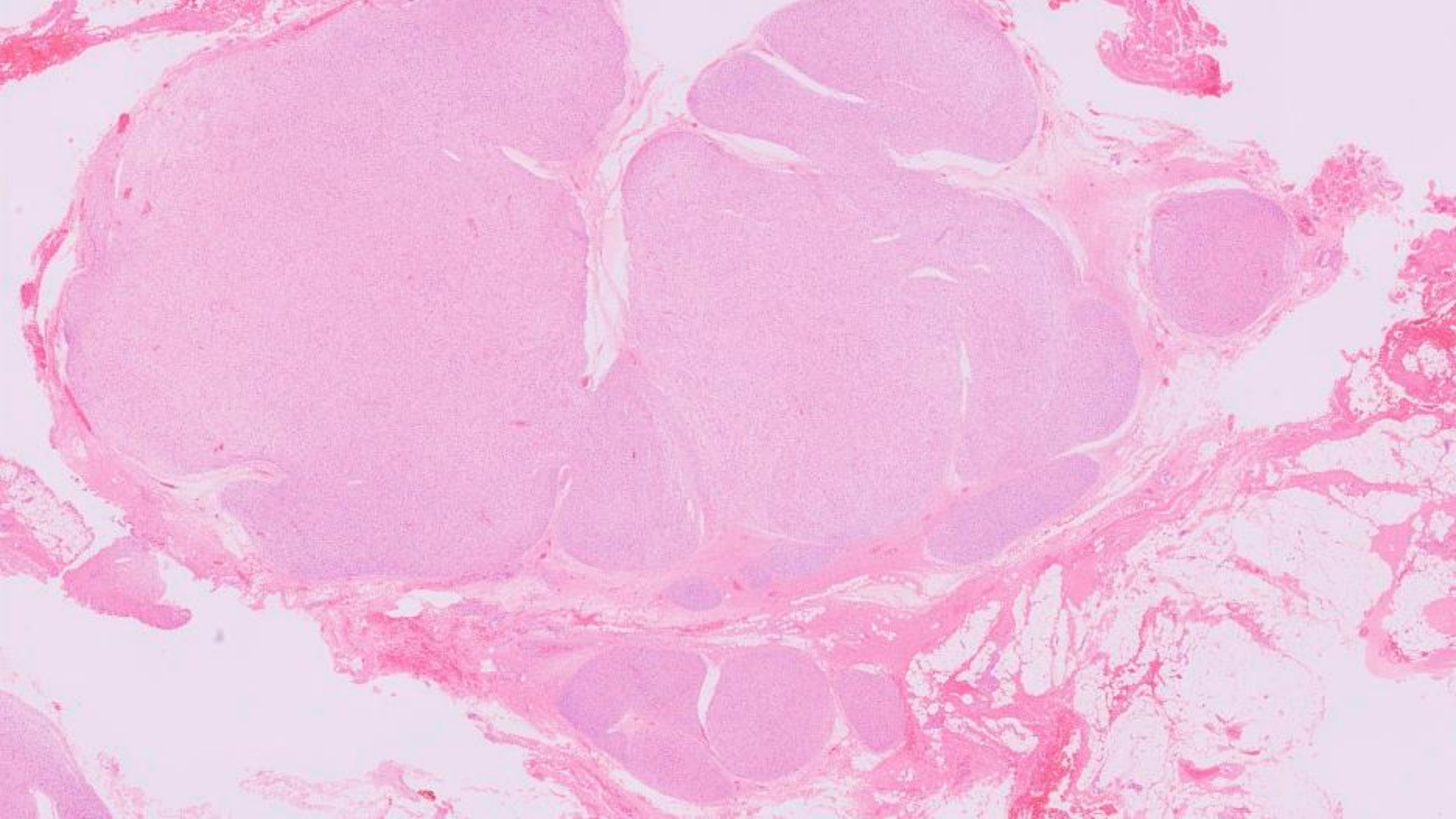
	Bothersome	Bad
CNS:	???	???
PNS:	???	???

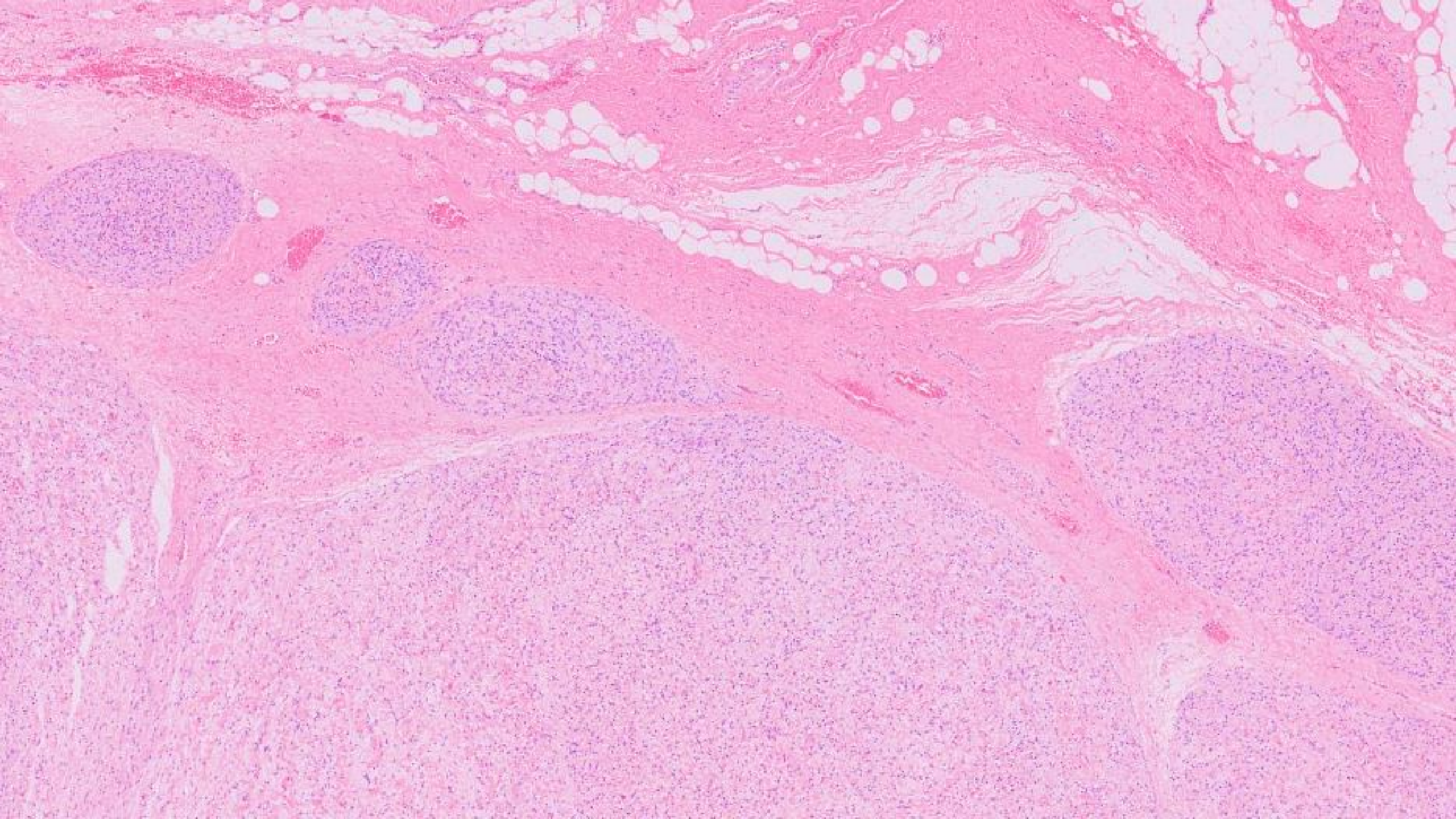
Case 4

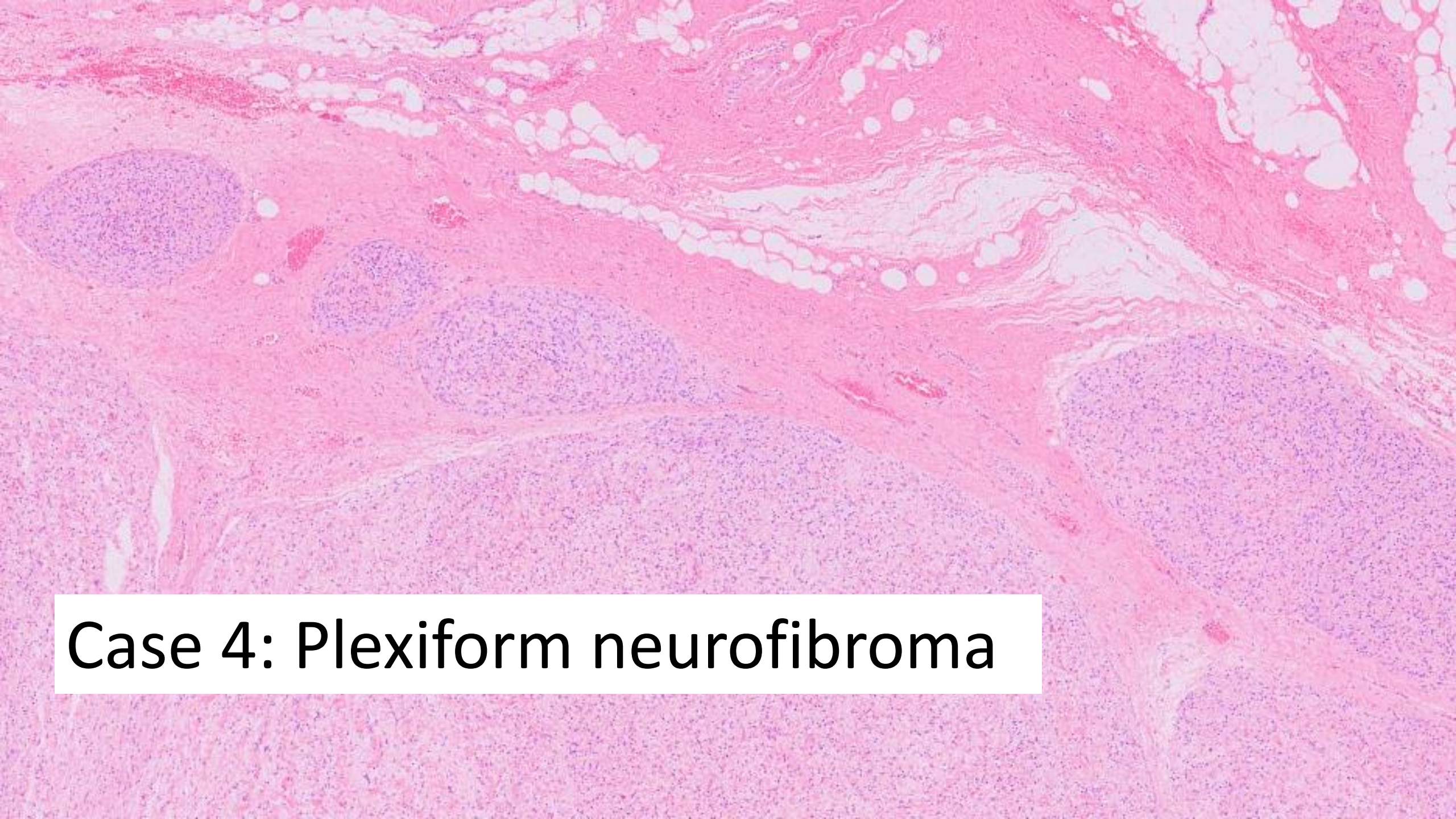
- 26-year-old woman with left upper limb numbness
- No formal NF1 diagnosis but physical exam reveals multiple café-au-lait macules and cutaneous neurofibromas
- Exam also reveals an ill-defined non-tender mass occupying the left posterior triangle of the neck
- Multilobulated lesion centered on the left brachial plexus extending into the supraclavicular soft tissues
- Undergoes excisional biopsy









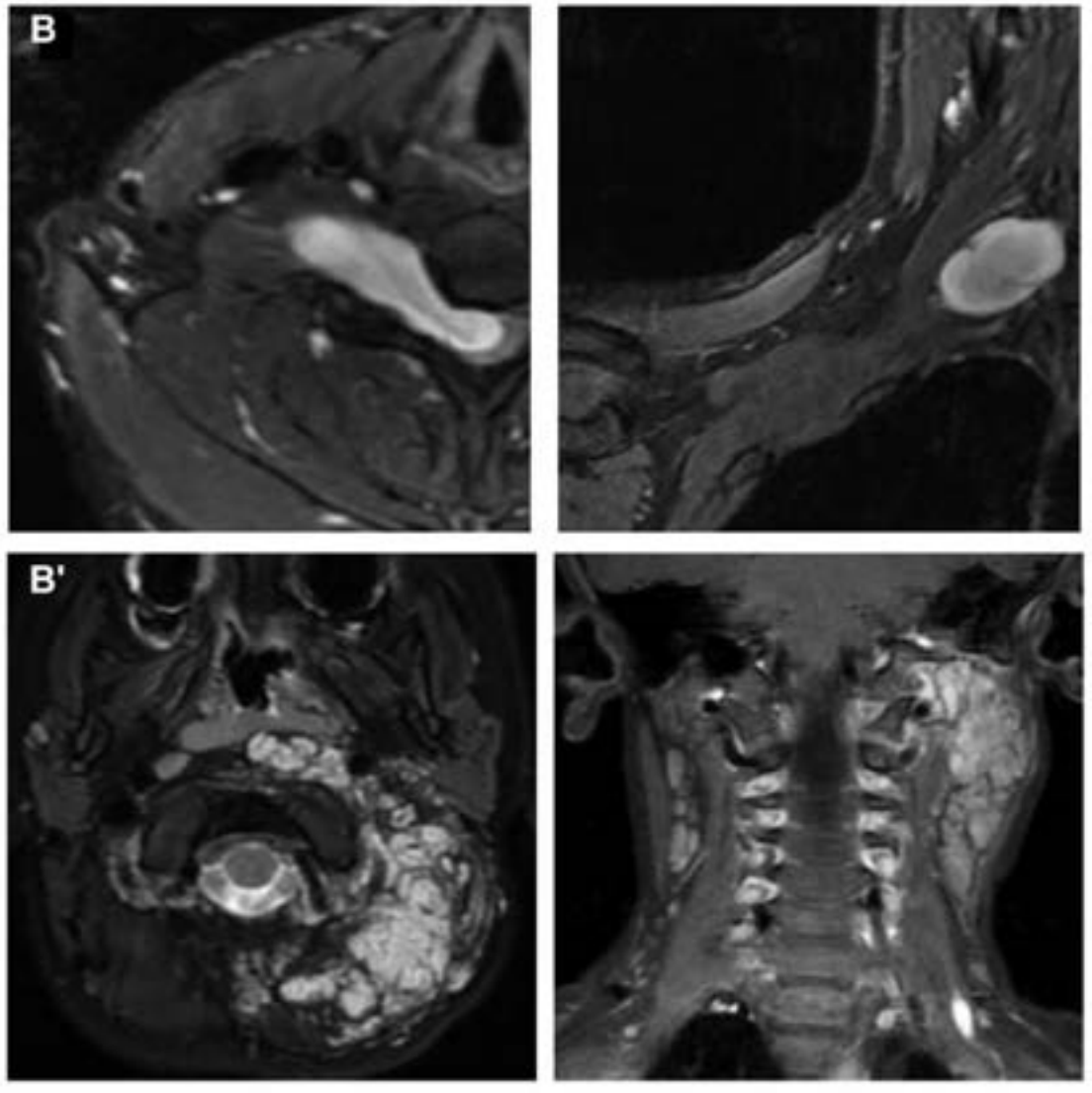


Case 4: Plexiform neurofibroma

NF1-associated nerve sheath tumors are clinicopathologically diverse

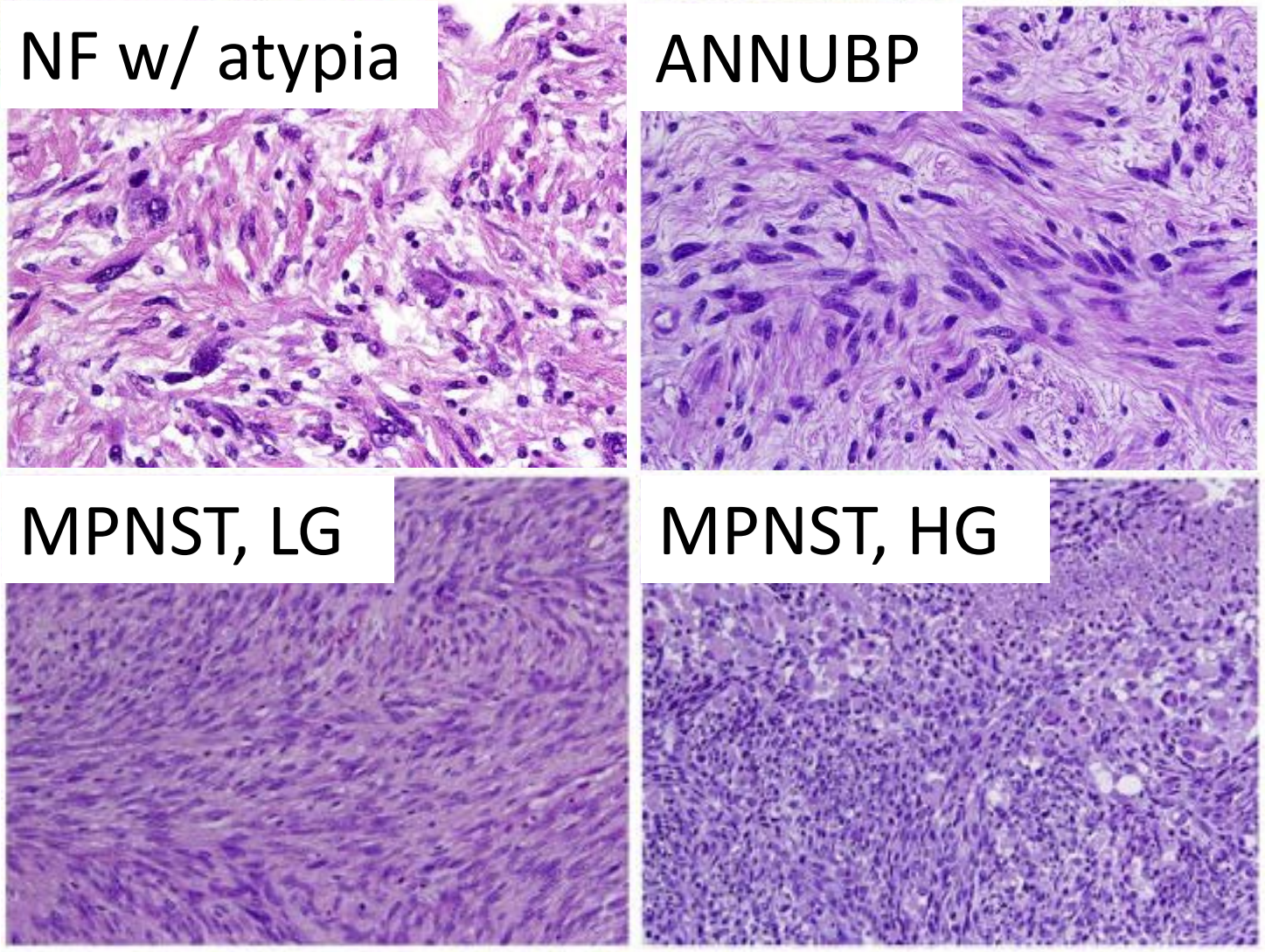
- Histologic definitions of ANNUBP and MPNST codified in the:
  - 2021 CNS WHO
  - 2022 BST WHO

- Incorporation of additional molecular strata only recently formalized



Vasudevan HN et al. *Neurosurgery*. 2021.

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

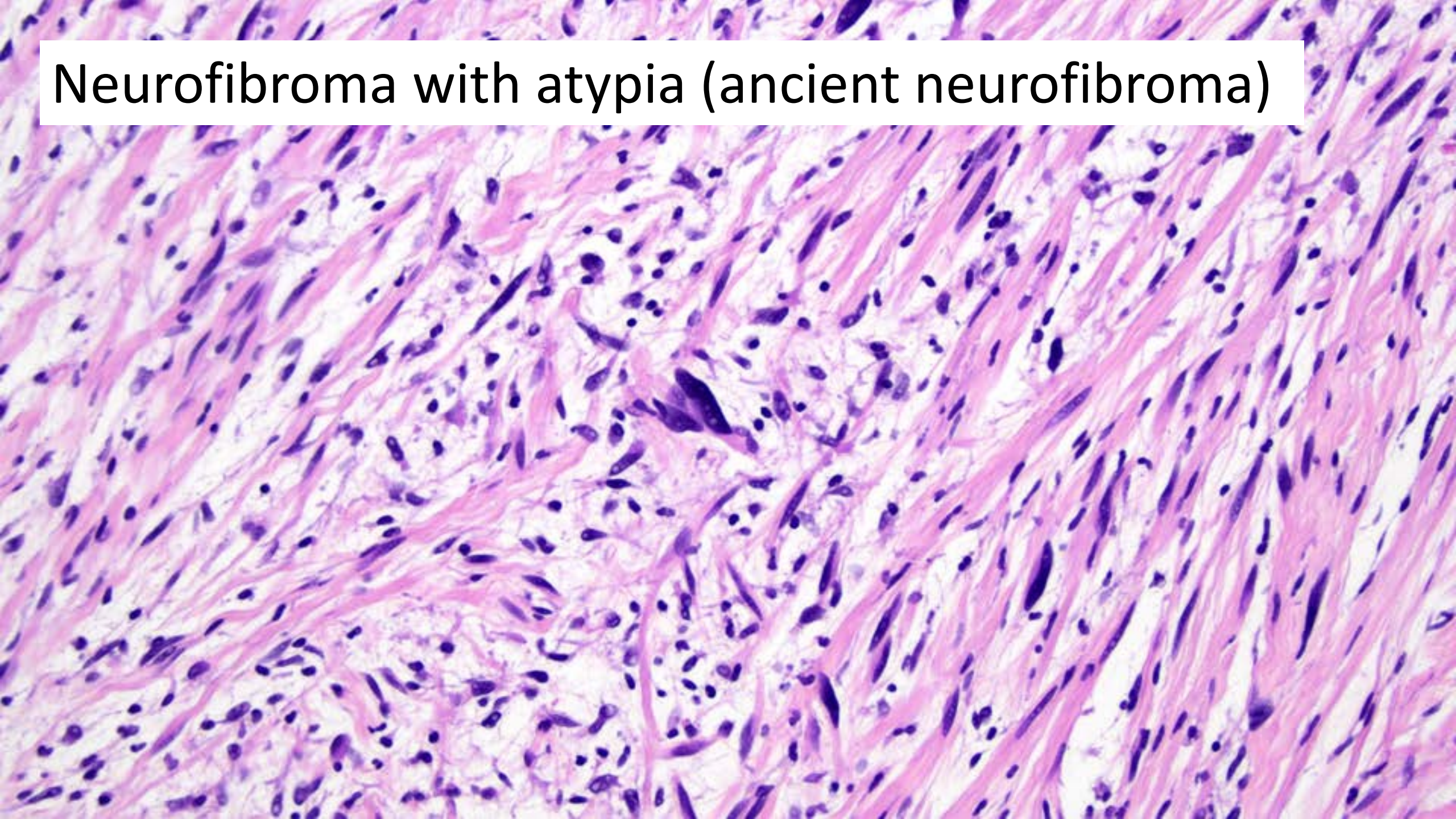


Miettinen MM et al. *Hum Pathol*. 2017.

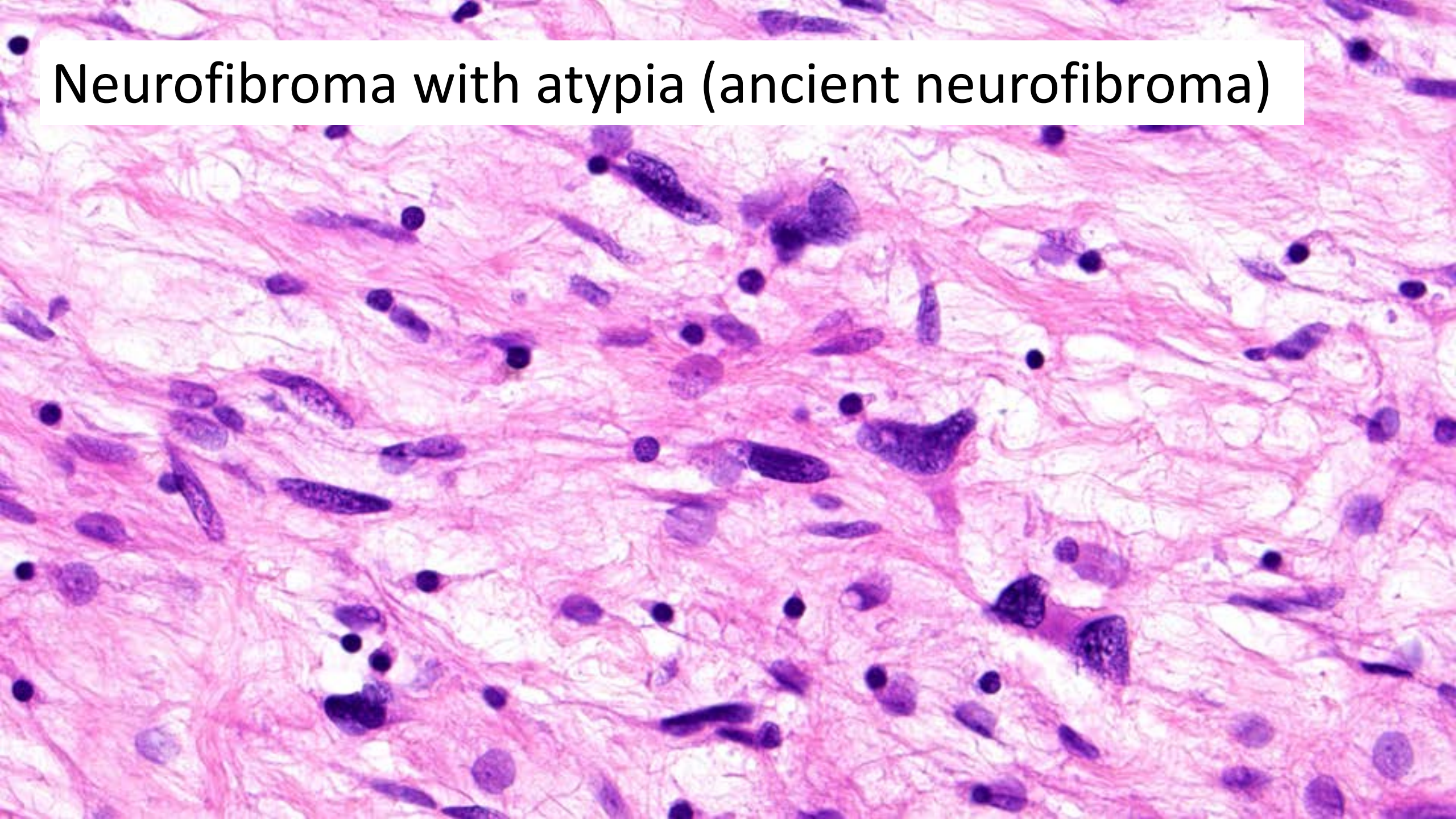
Table Proposed nomenclature for the spectrum of NF1-associated nerve sheath tumors

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

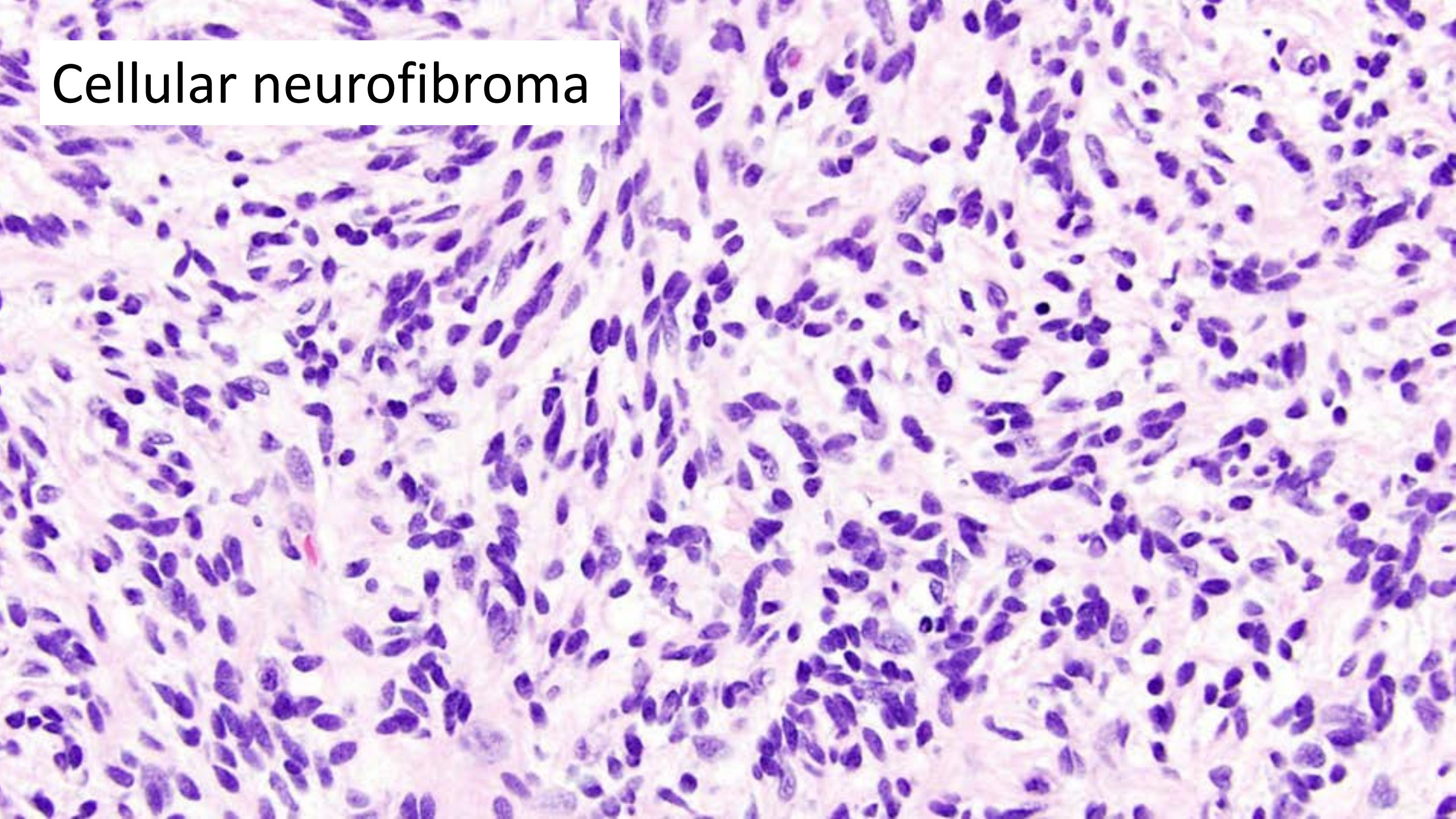
Neurofibroma with atypia (ancient neurofibroma)



Neurofibroma with atypia (ancient neurofibroma)

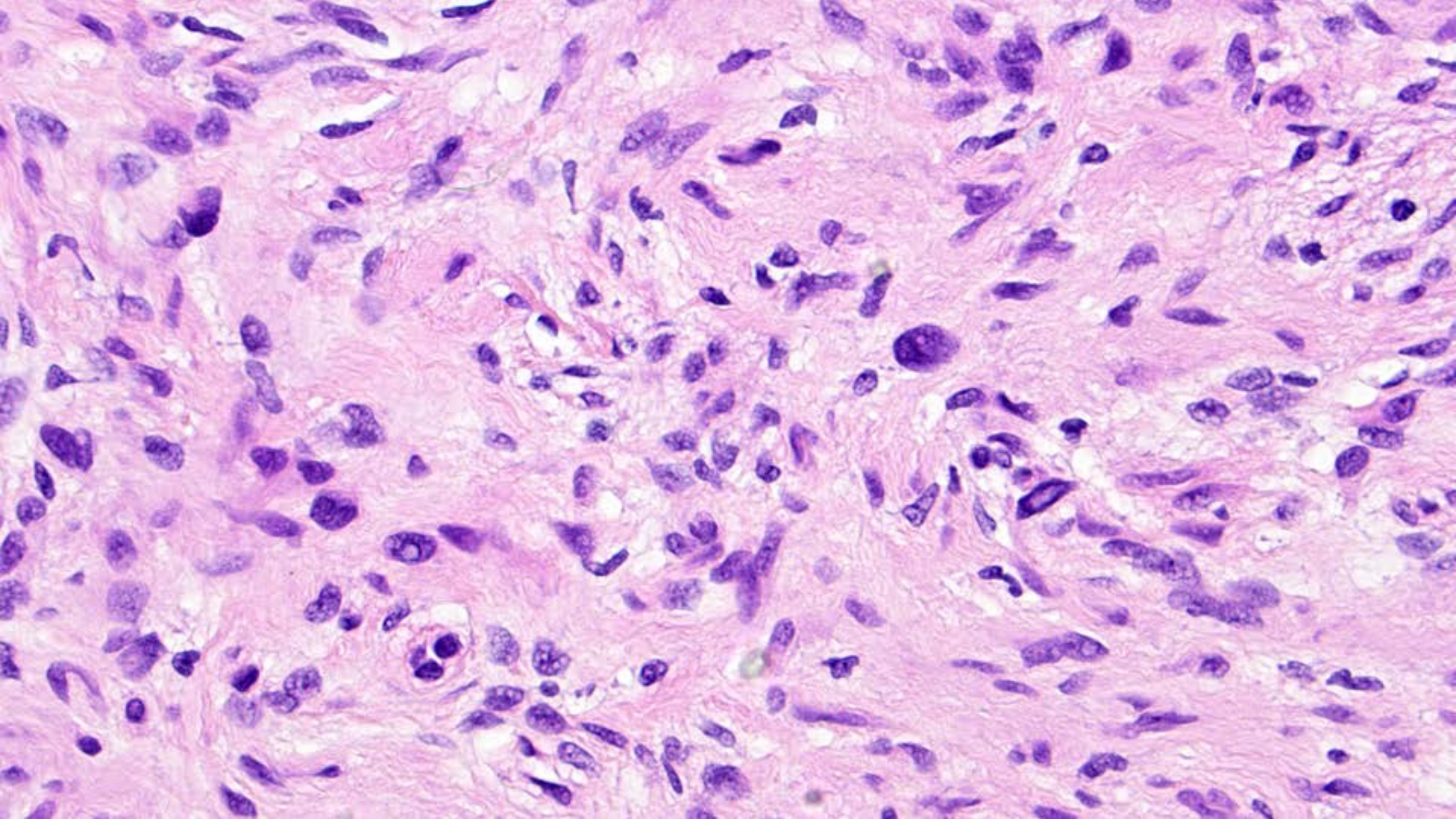


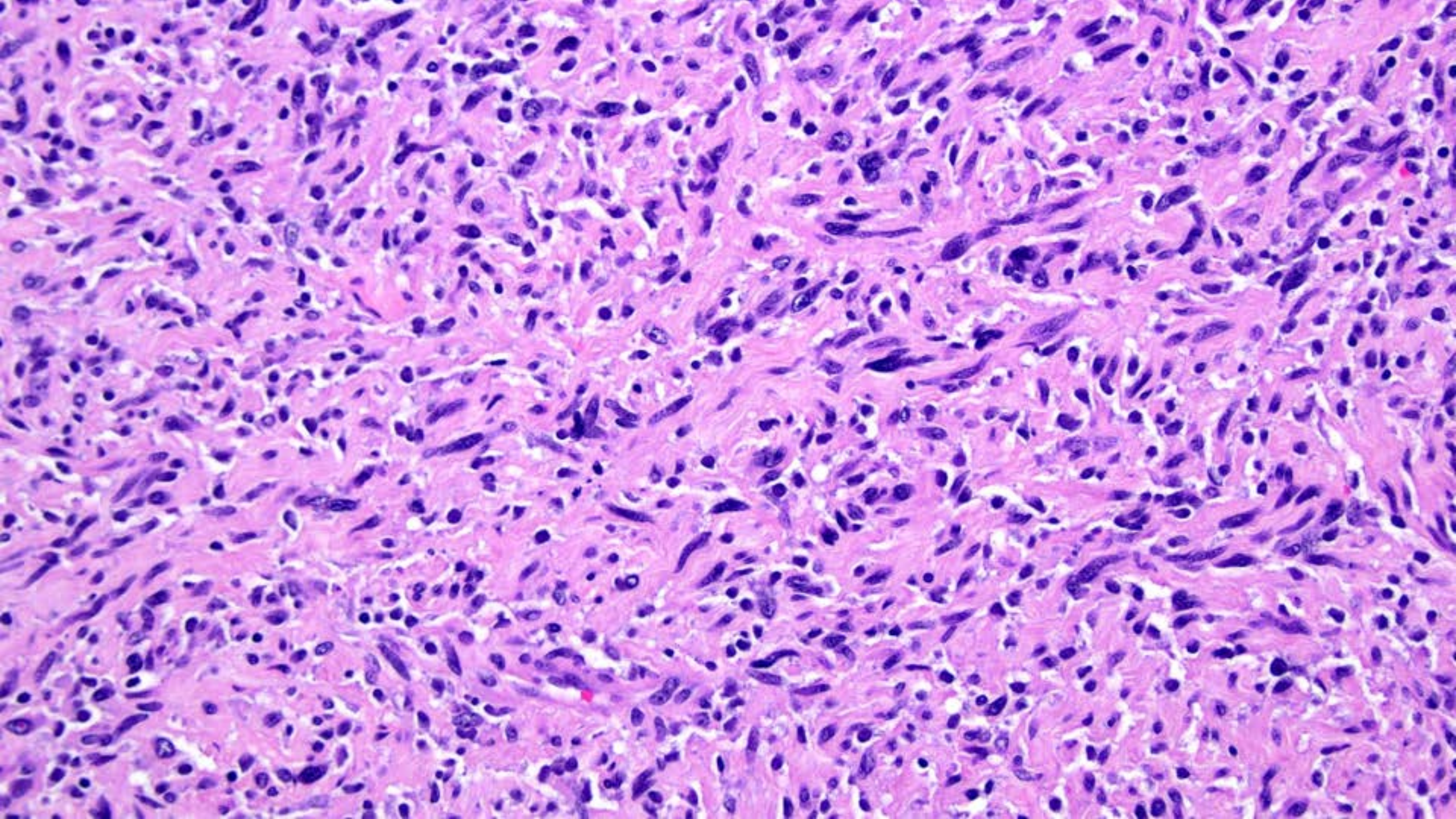
Cellular neurofibroma

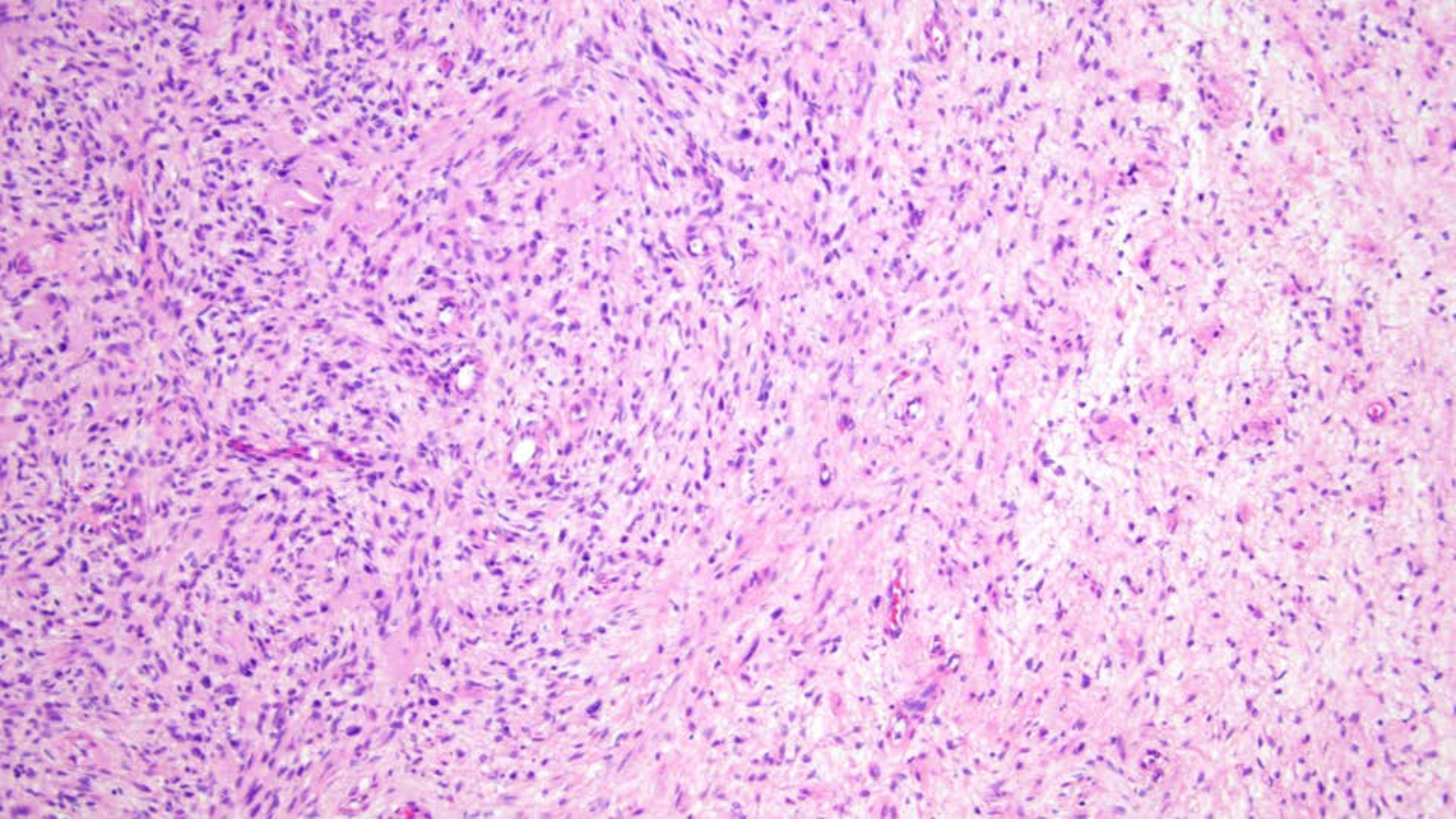


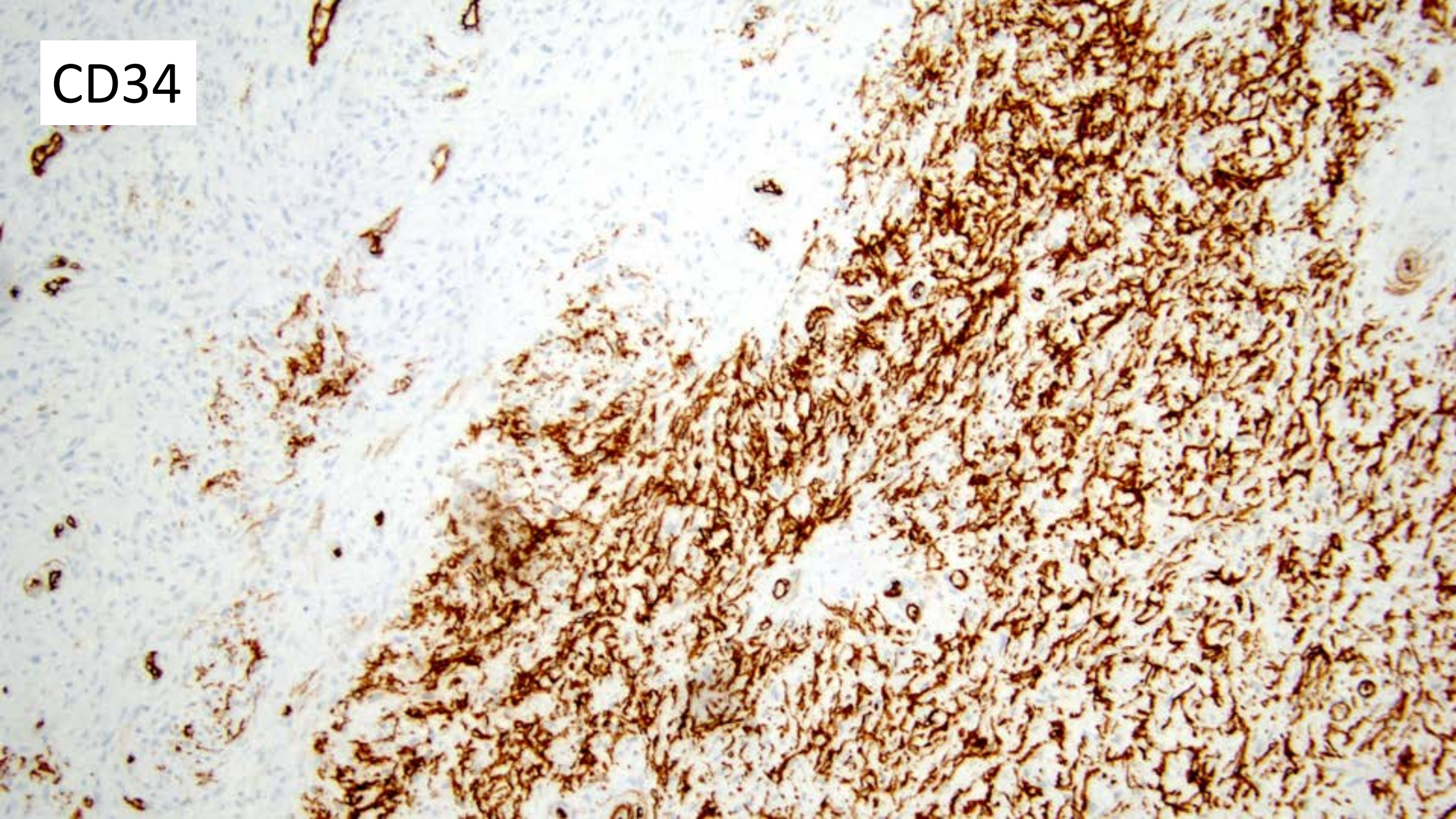
Case 5

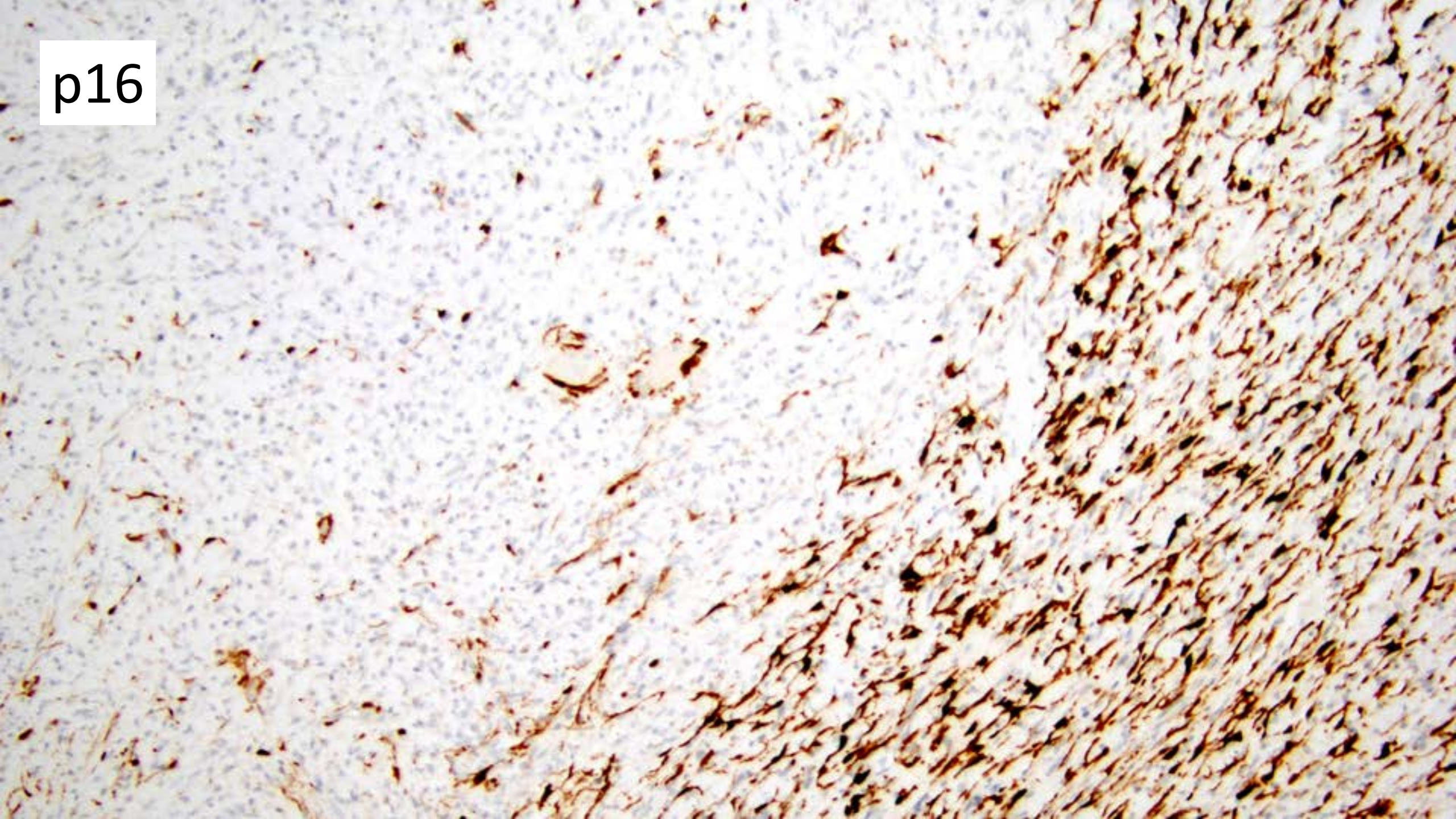
- 35-year-old man with increasing pain and discomfort in a longstanding right posterior thigh mass
- NF1 diagnosed during childhood, known plexiform neurofibroma involving the right sciatic nerve monitored with serial imaging
- Fusiform enlargement of the sciatic nerve with new nodular focus with avid enhancement and reduced diffusion compared with prior examinations
- Moderately increased FDG uptake within the nodular component
- Undergoes diagnostic core biopsy





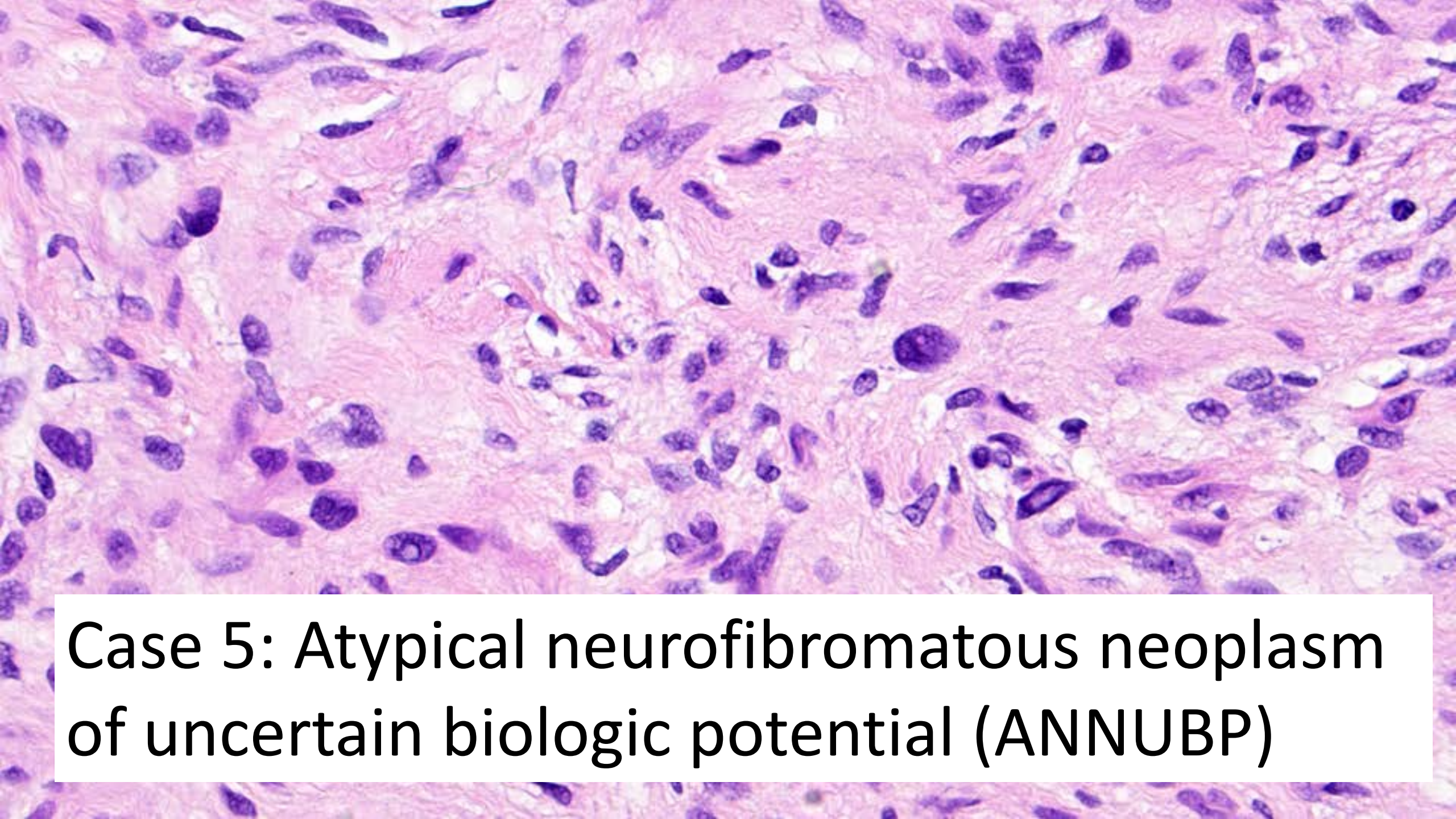



CD34


p16

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

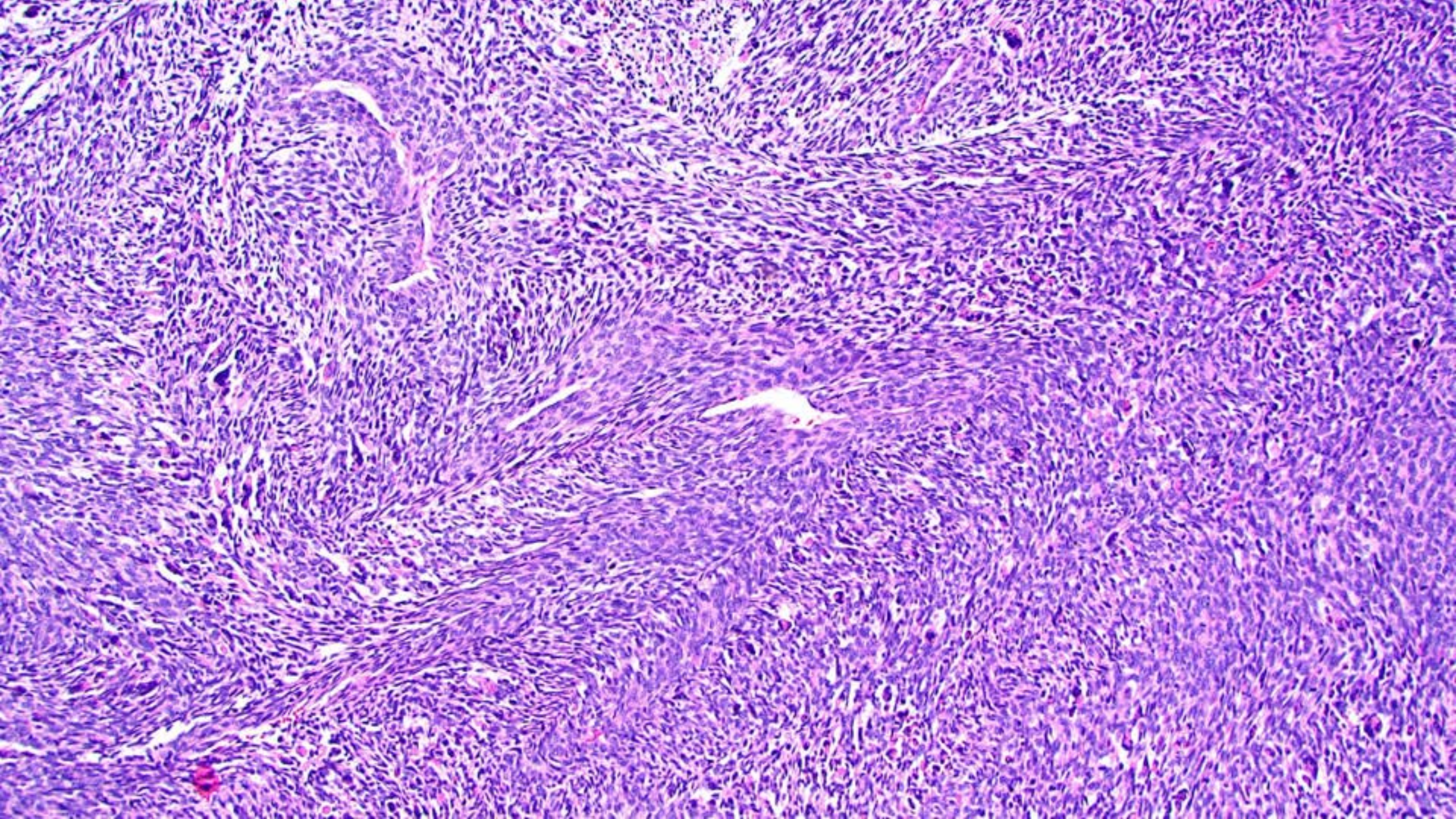
Miettinen MM et al. *Hum Pathol*. 2017.

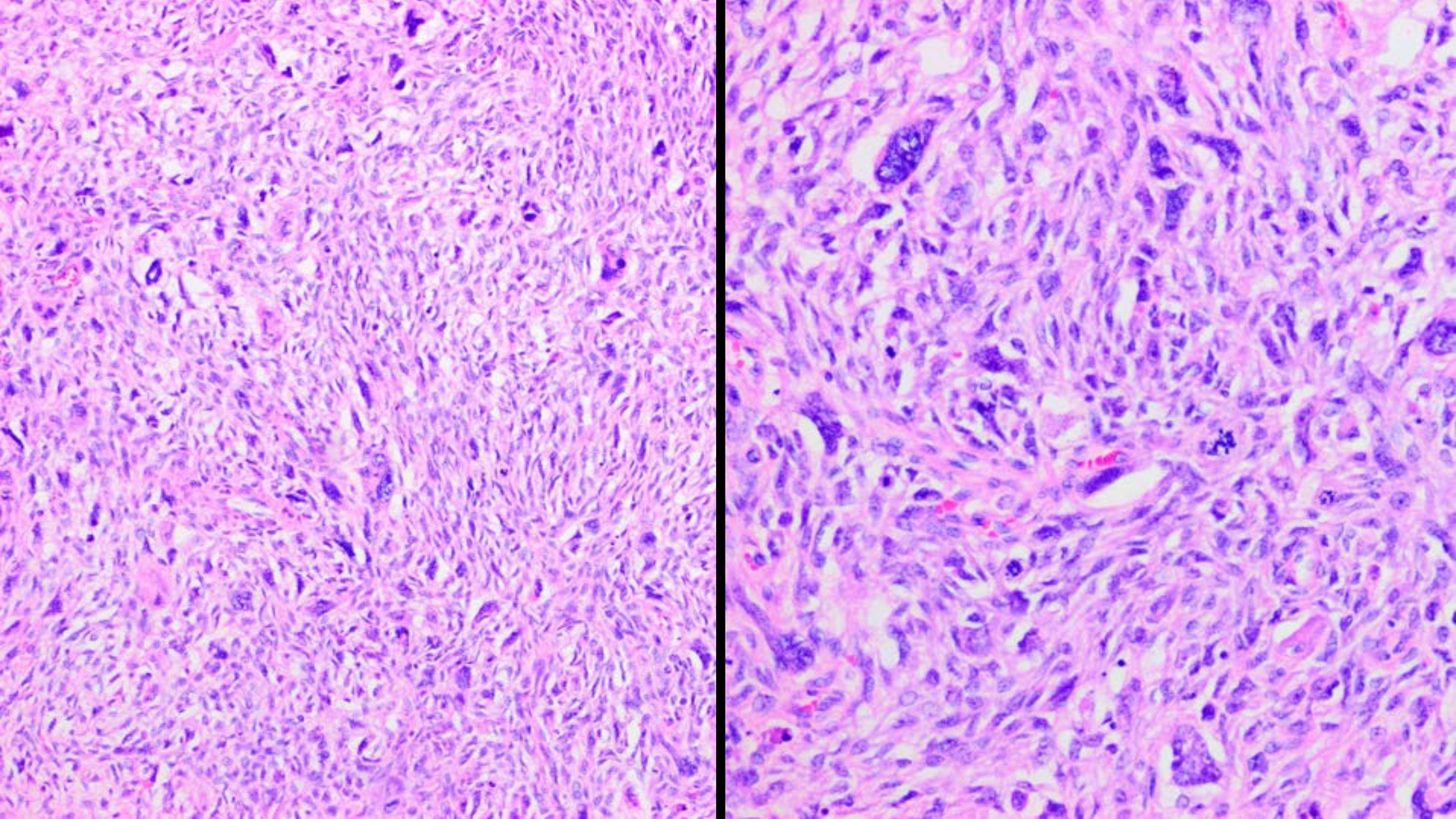


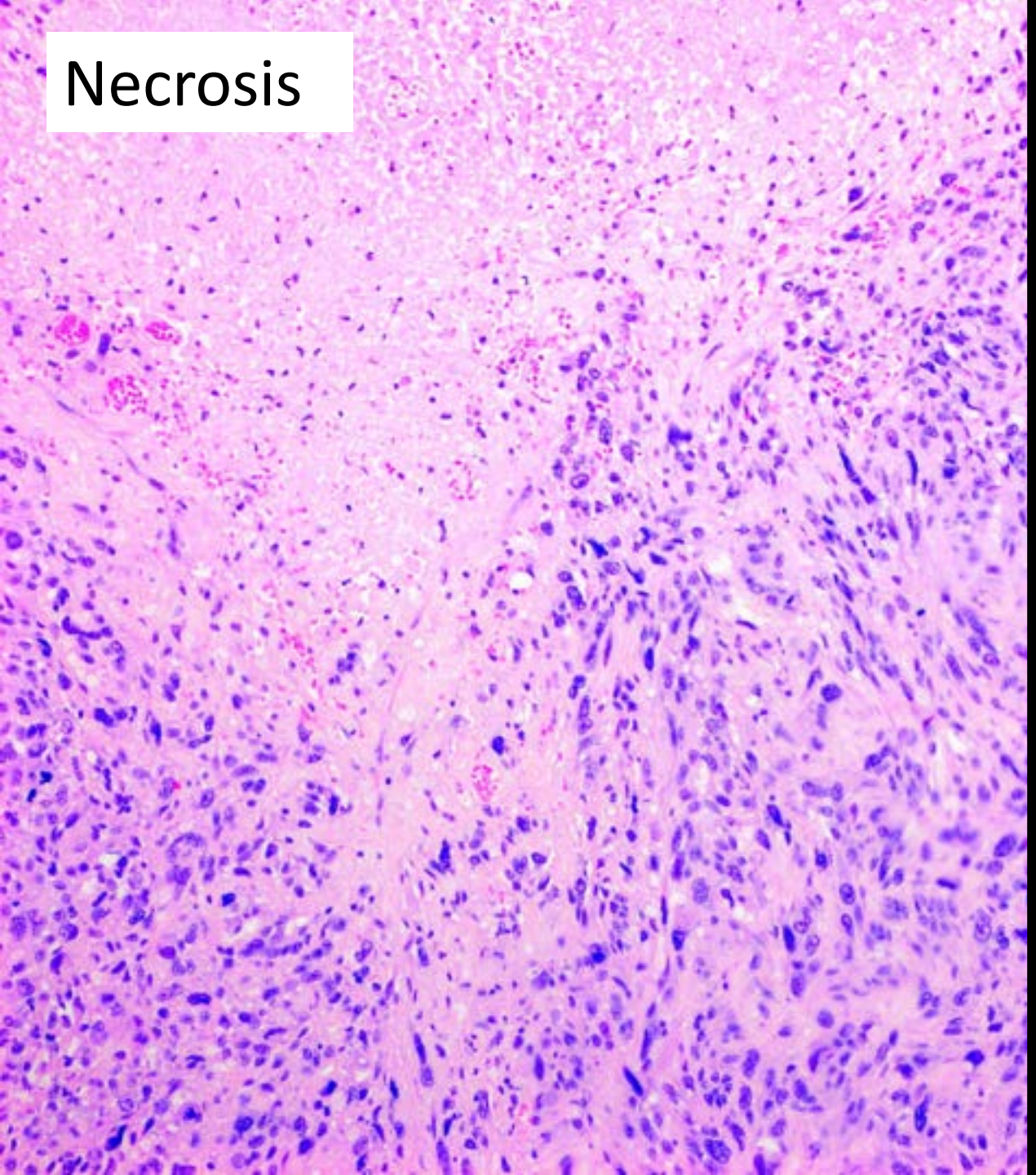
Case 5: Atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP)

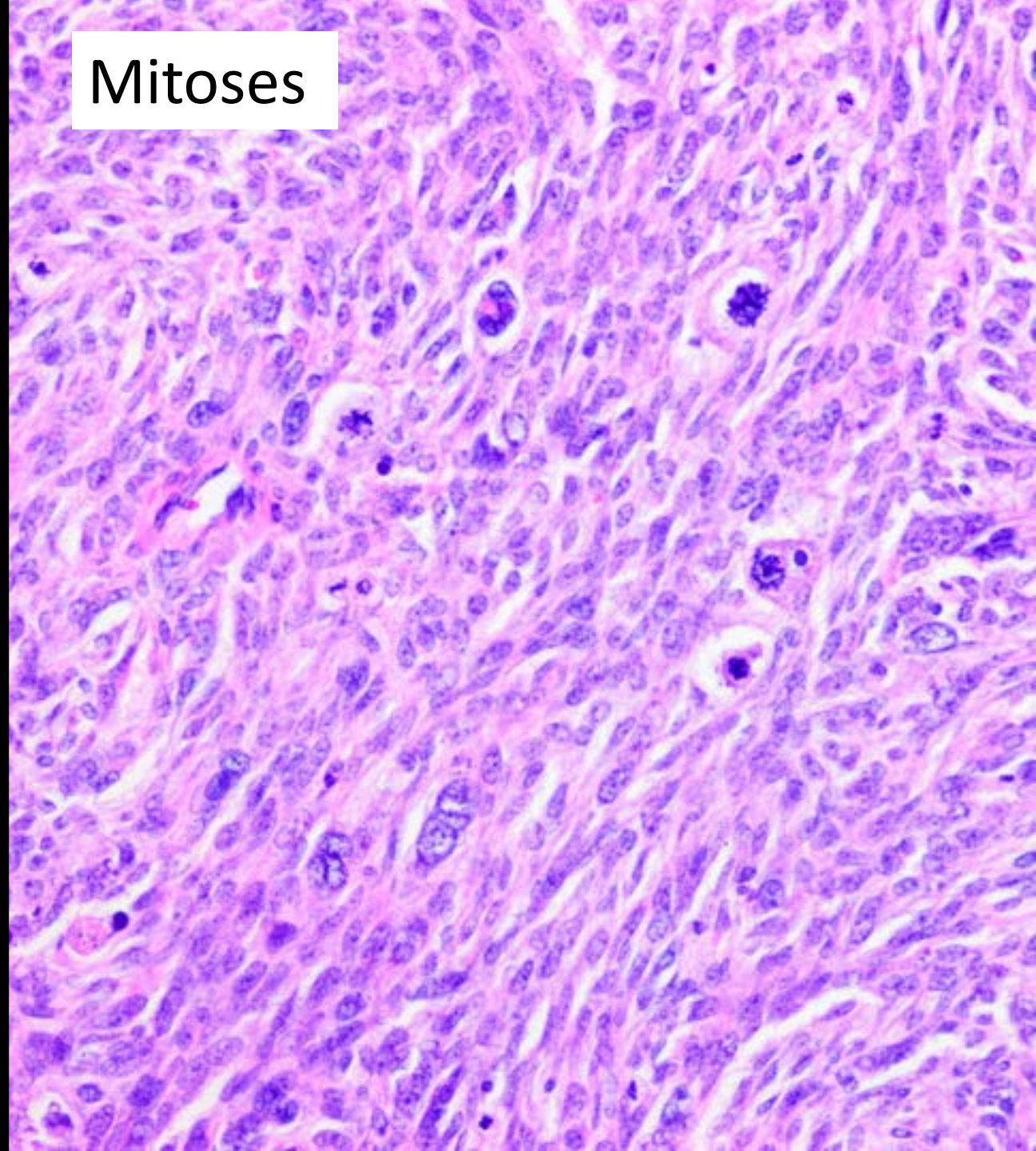
Case 6

- 33-year-old woman with rapidly enlarging painful left thigh mass
- NF1 diagnosed during childhood, known plexiform neurofibroma involving the left sciatic nerve monitored with serial imaging
- Heterogeneous mass arising from the left sciatic nerve with rapid interval growth
- Markedly increased FDG uptake within the lesion
- No distant metastatic disease identified
- Undergoes resection



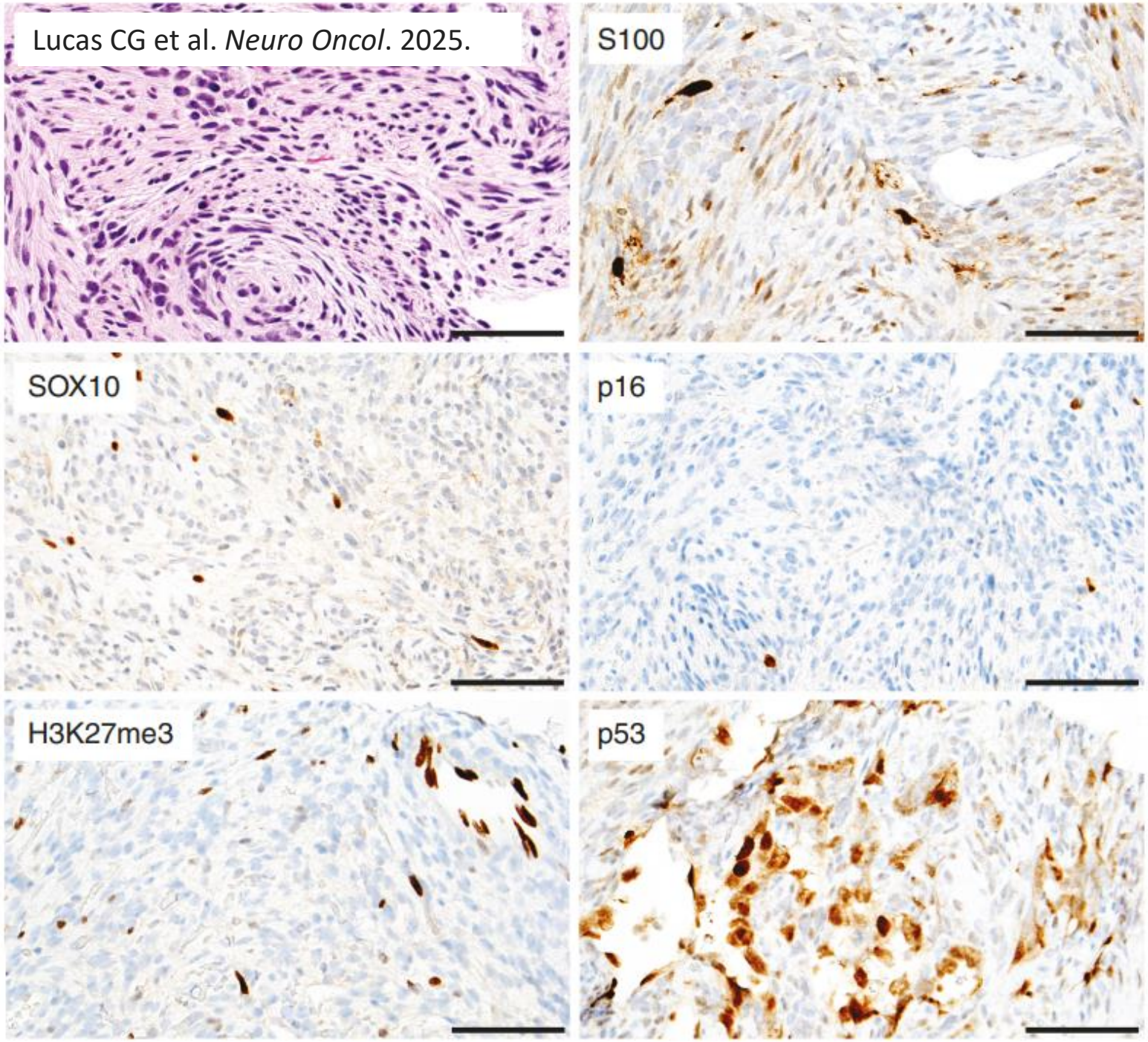


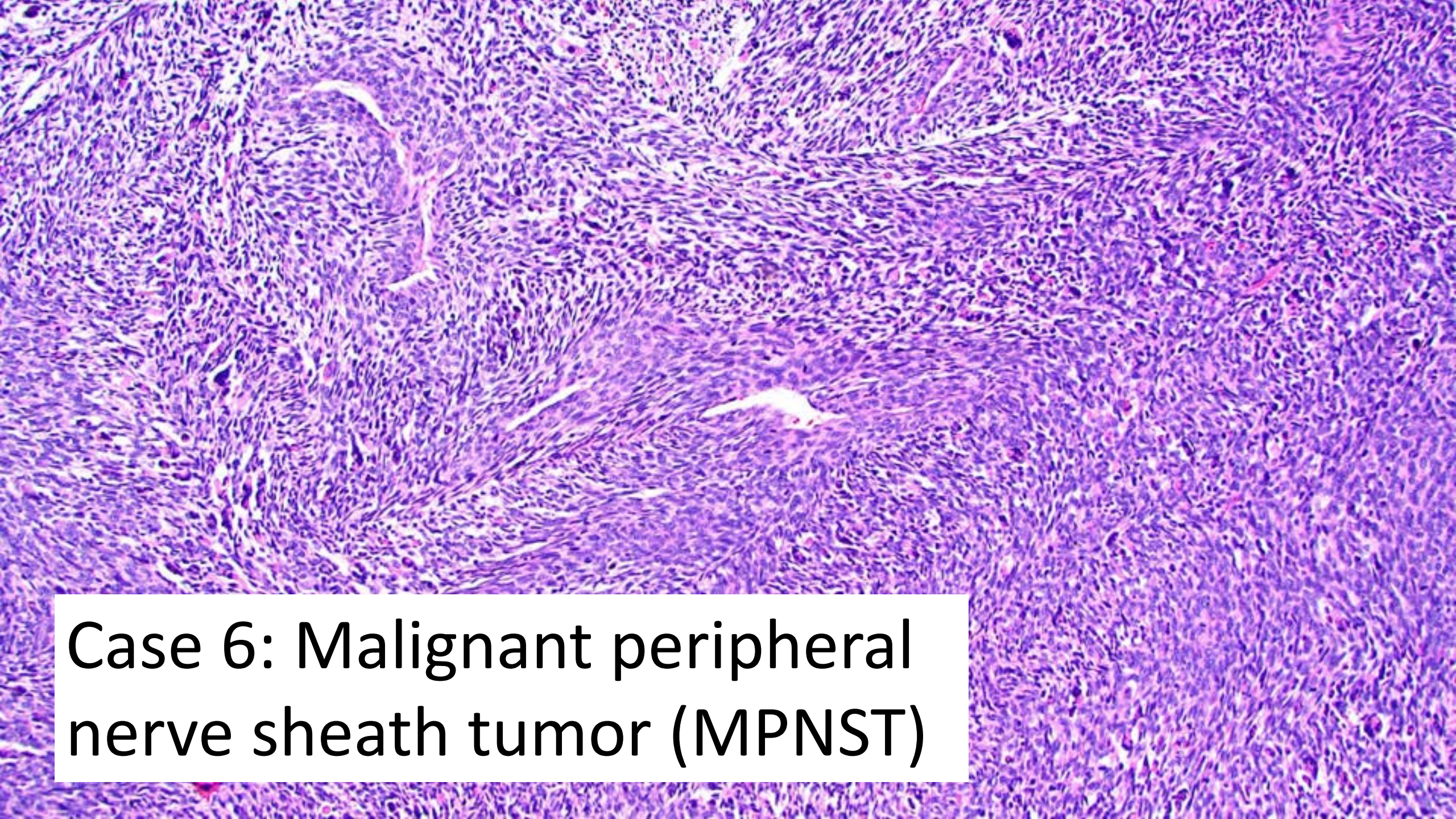

Necrosis


Mitoses

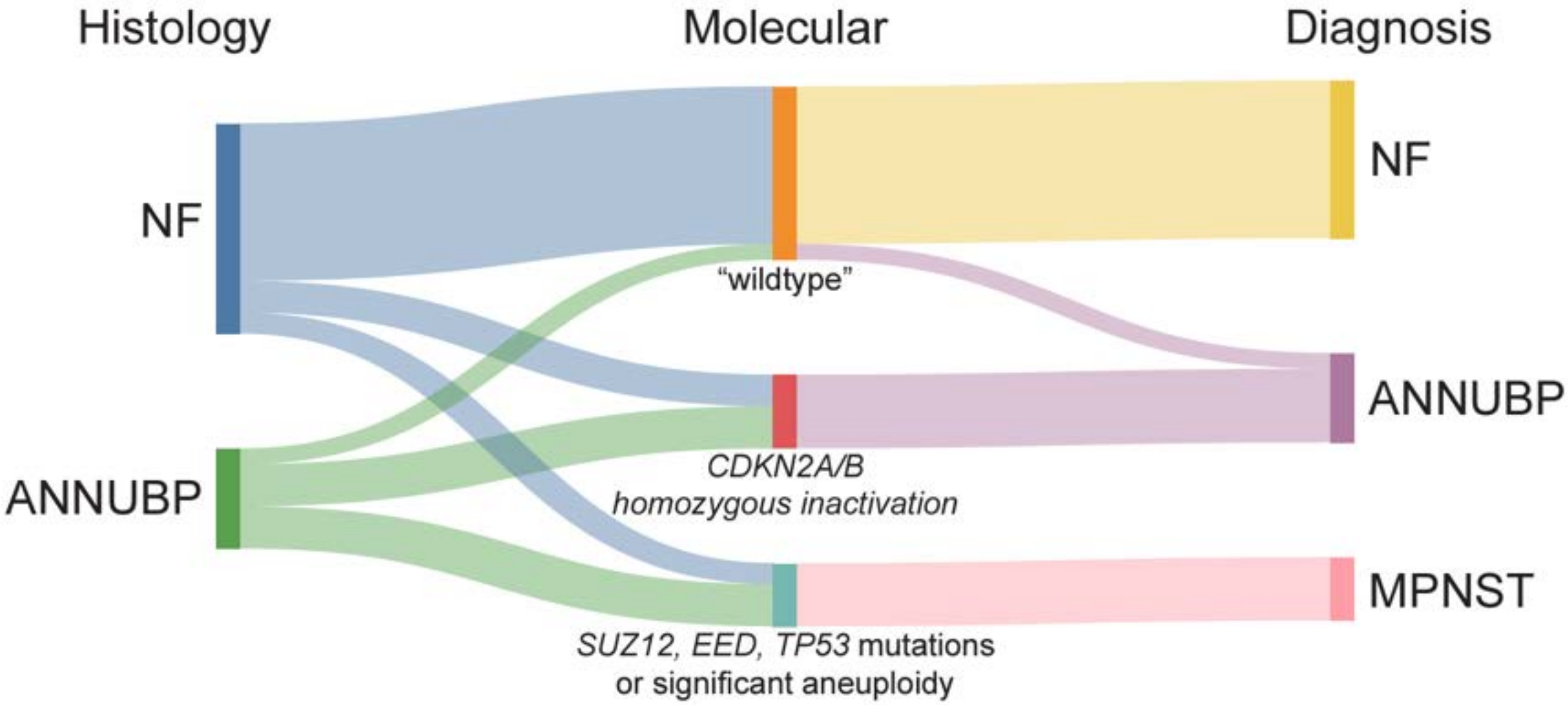
MPNST, low-grade	Features of ANNUBP, but with mitotic index of 3-9/10 HPFs and no necrosis
MPNST, high-grade	MPNST with at least 10 mf/10 HPFs or 3–9 mf/10 HPFs combined with necrosis

Miettinen MM et al. *Hum Pathol*. 2017.


Lucas CG et al. *Neuro Oncol*. 2025.
S100
SOX10
p16
H3K27me3
p53


Case 6: Malignant peripheral
nerve sheath tumor (MPNST)

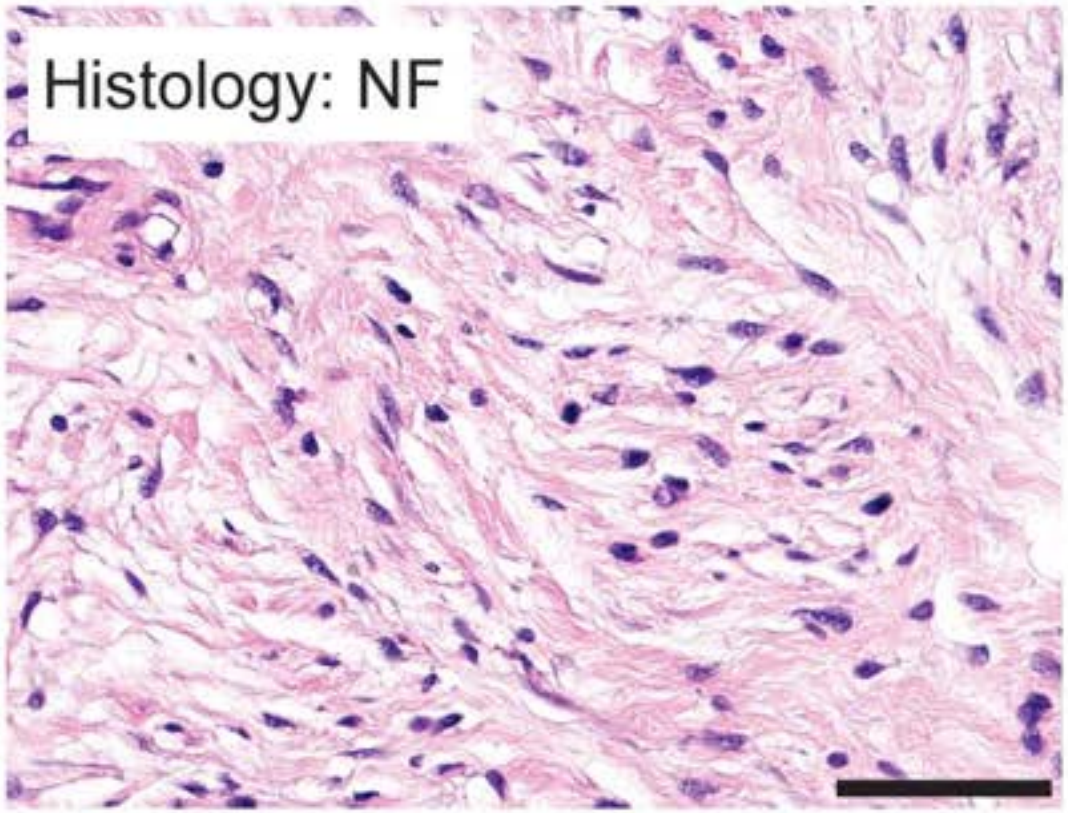
Integrated diagnostic approach

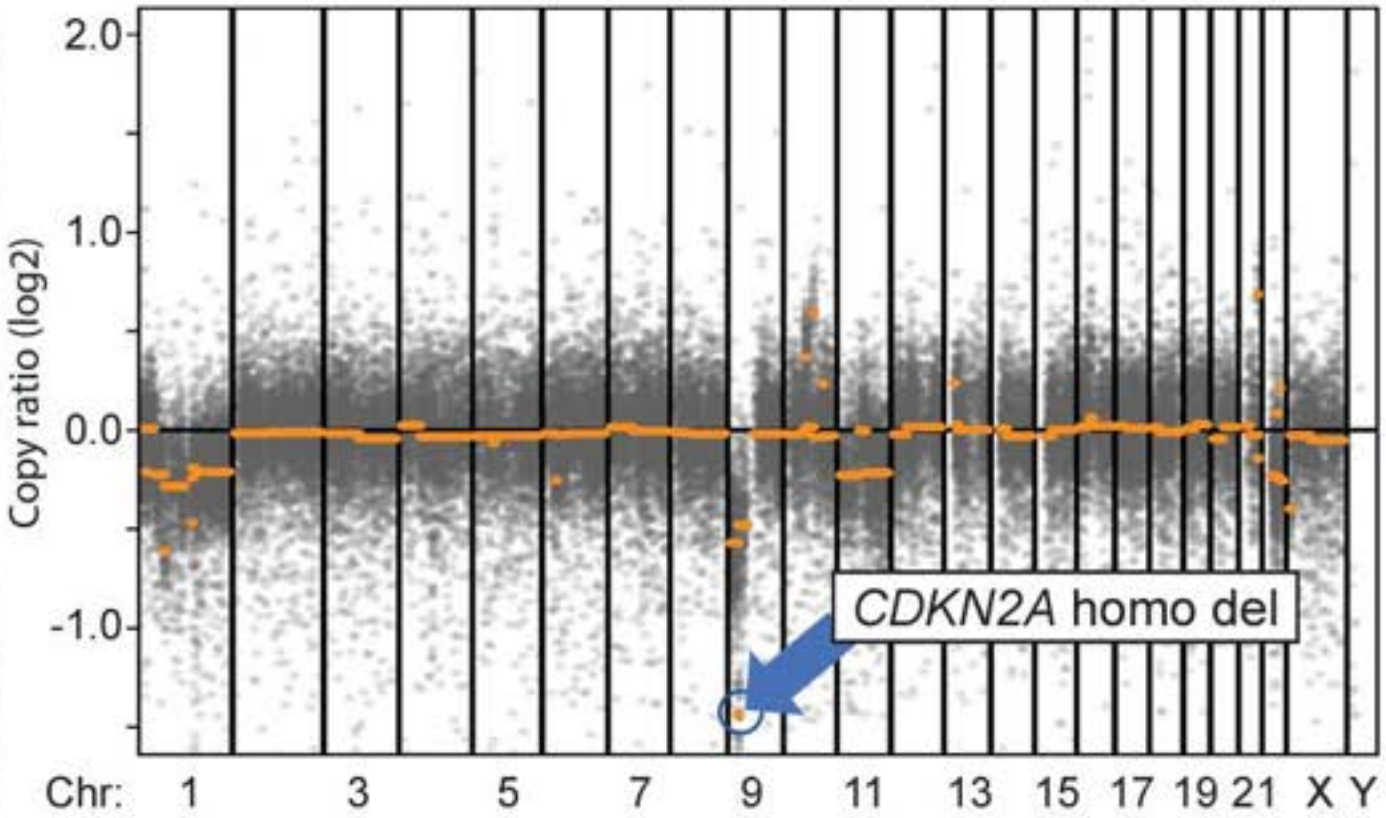


Lucas CG et al. *Neuro Oncol*. 2025.

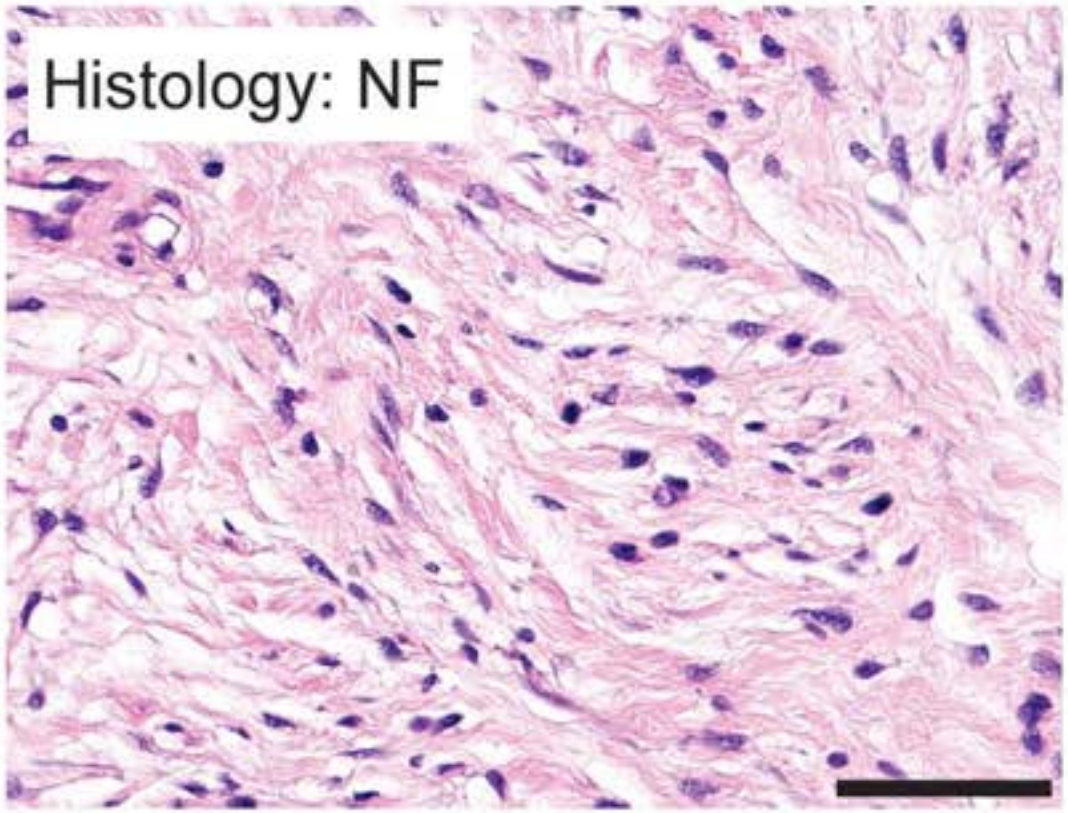
Case 4 (revisited)

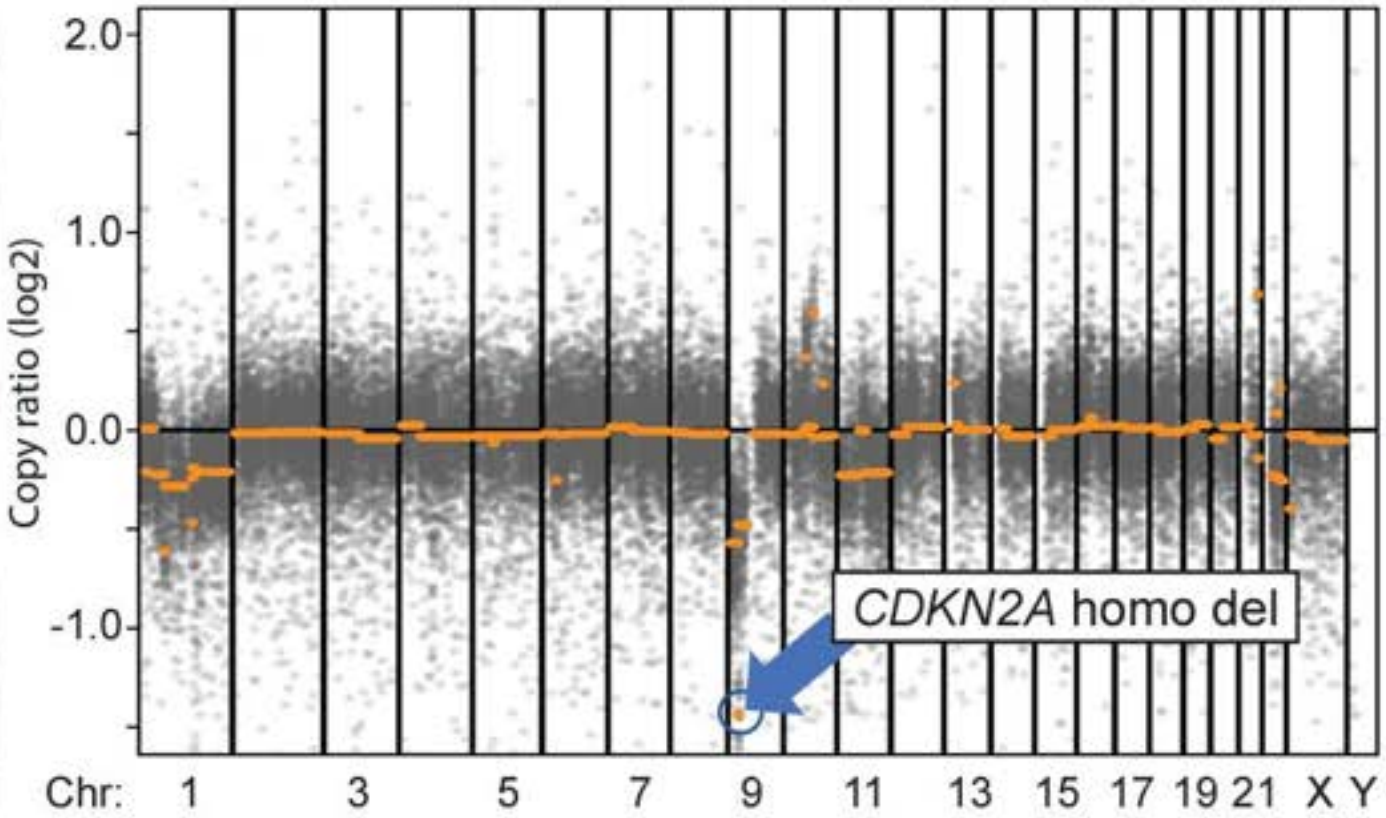
- 26-year-old woman
- multilobulated lesion centered on the left brachial plexus
- excisional biopsy consistent with plexiform neurofibroma





Molecular: *NF1* p.E1550*, *NF1* p.W599*, *CDKN2A* homo del





Molecular: *NF1* p.E1550*, *NF1* p.W599*, *CDKN2A* homo del

Proposed integrated diagnosis: **ANNUBP**

Framework for adequate interventional radiology and surgical sampling:

*Screen all non-cutaneous neurofibromas undergoing diagnostic biopsy to evaluate for molecular features of ANNUBP or MPNST

Pre-procedure imaging considerations:	
	Targeting of radiologically-concerning but surgically accessible areas, multiple regions if possible
Sampling considerations:	
	Use 14G to 18G biopsy needles
	Obtain at least six core biopsies if feasible
	Clearly label separate containers with biopsy site of origin (*e.g.* region #1, FDG-PET avid region)
Tissue processing considerations:	
	No more than two cores per formalin-fixed, paraffin-embedded block
	Evaluation by subspecialized pathologist

Lucas CG et al. *Neuro Oncol*. 2025.

Overall take-home points

- Our understanding of tumorigenesis (and corresponding classification schemes) for NF1-associated nervous system tumors continues to evolve as we utilize contemporary omic approaches
- Surrogate markers can help facilitate accurate diagnosis in our daily practice, but molecular studies should be performed and integrated appropriately

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AANP

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- Johns Hopkins NF1 Biospecimen Repository
- Johns Hopkins Brain and Eye Tumor Research Group
- Pilocytic/Pilomyxoid Fund
  - Lauren's First and Goal
  - Stick It to Brain Tumors