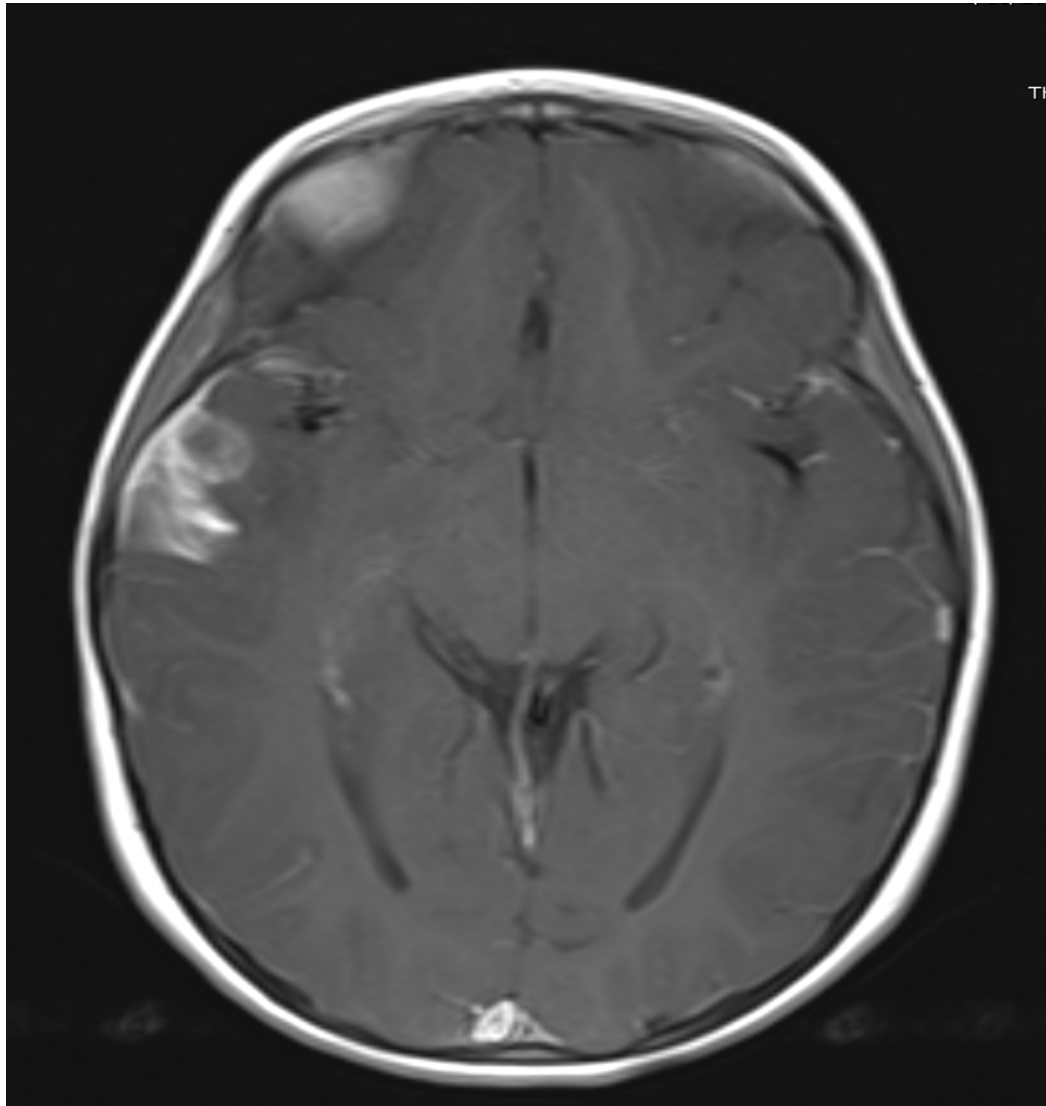


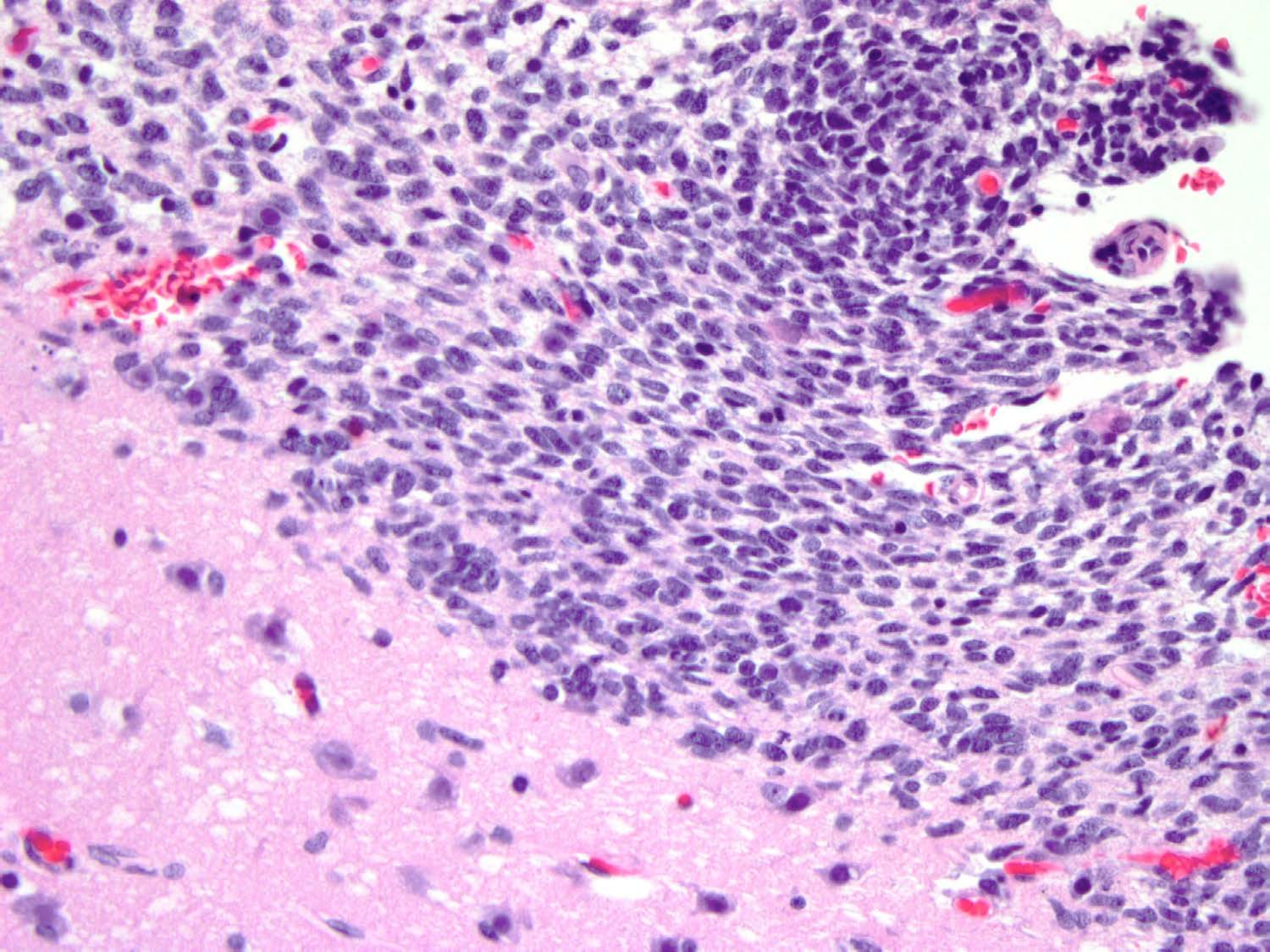


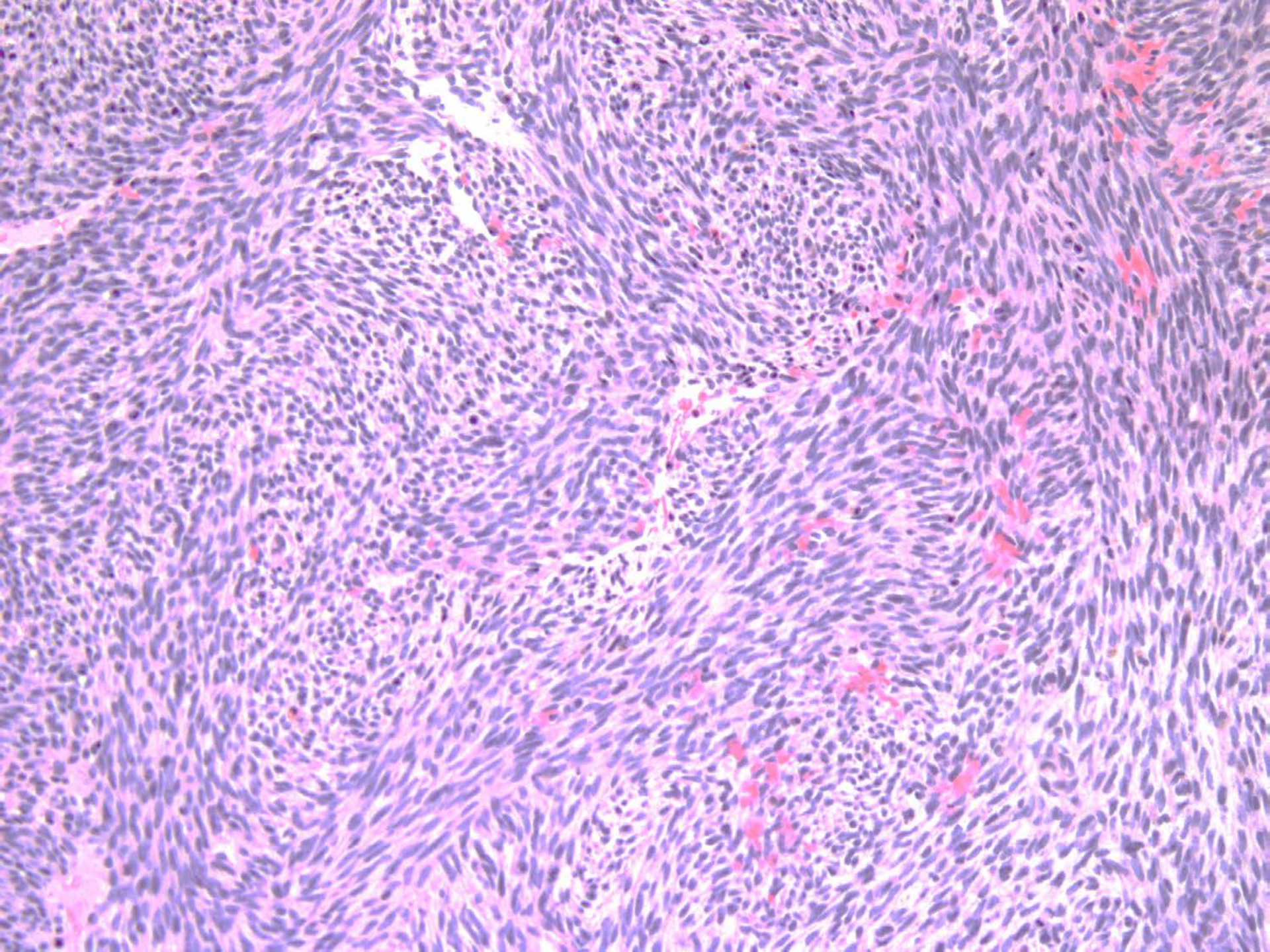
DSS 2017-9

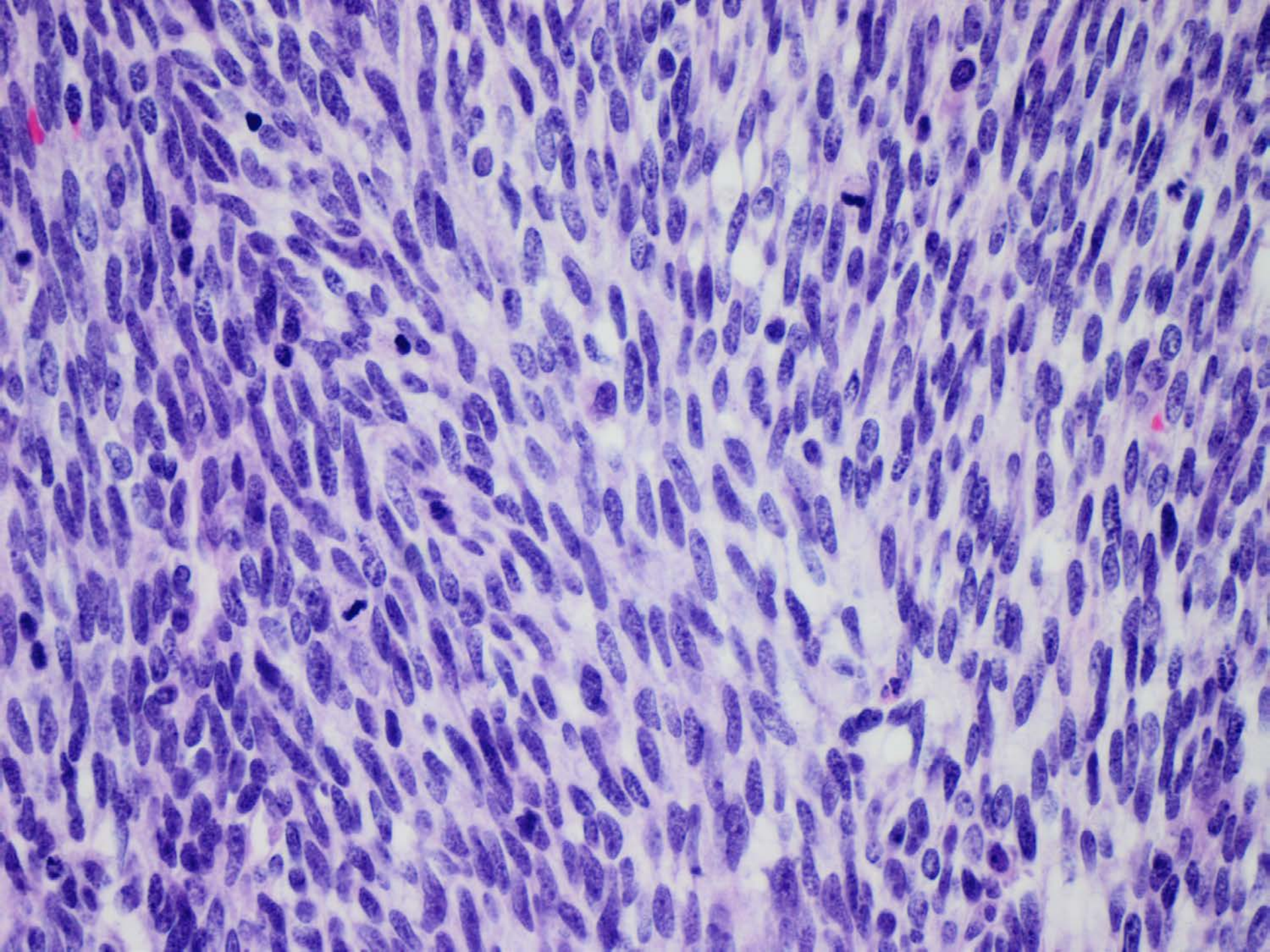
Sanda Alexandrescu M.D, Sara Vargas M.D
Boston Children's Hospital

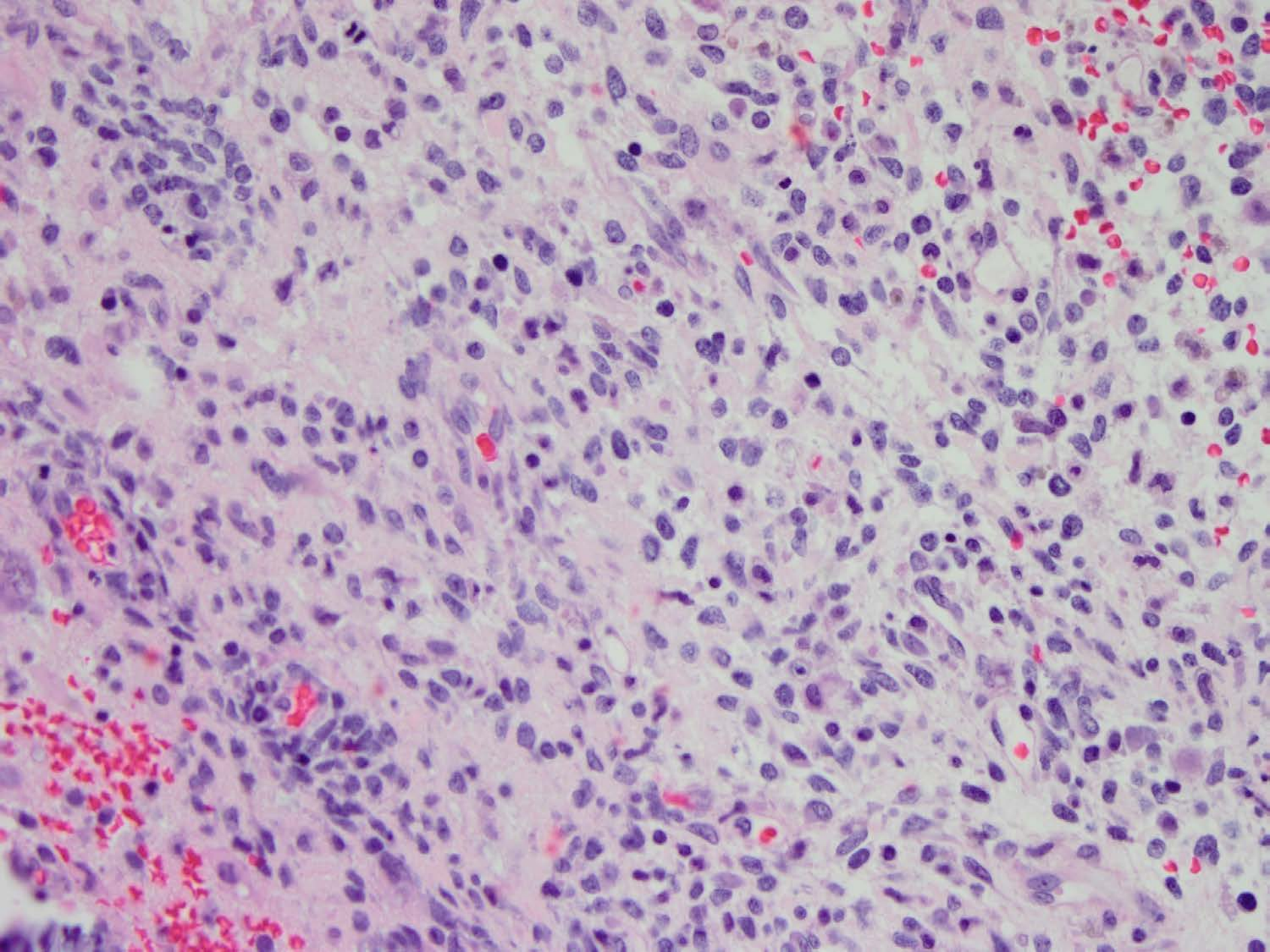
3 year-old girl with a short history of headaches











Differential diagnosis?

Immunohistochemical stains?

Molecular tests?

Final diagnosis?

Differential Diagnosis

High-grade glioma/gliosarcoma

Anaplastic meningioma

Malignant hemangiopericytoma

Rhabdoid tumor

Synovial sarcoma

Malignant peripheral nerve sheath tumor

Malignant triton tumor

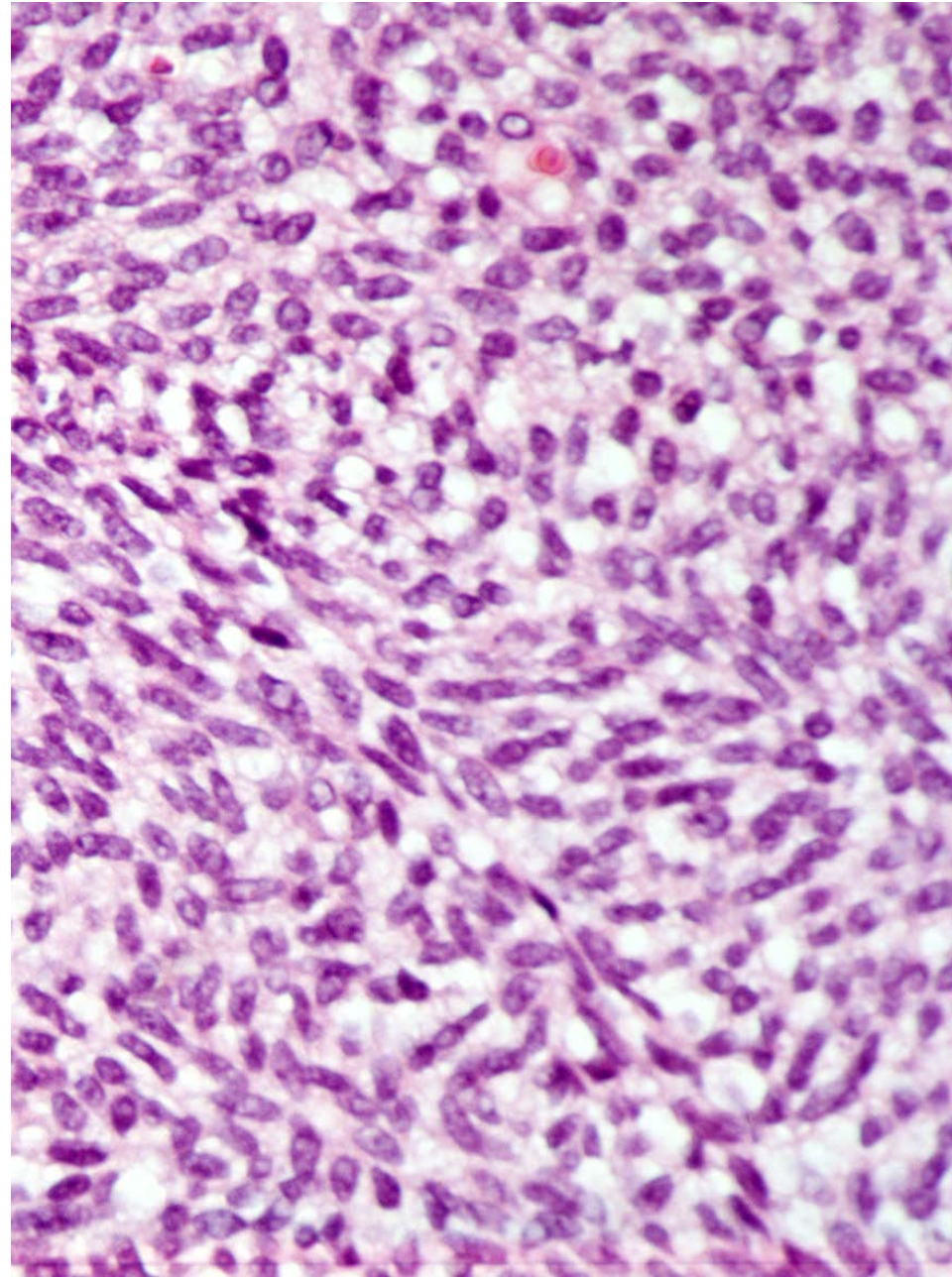
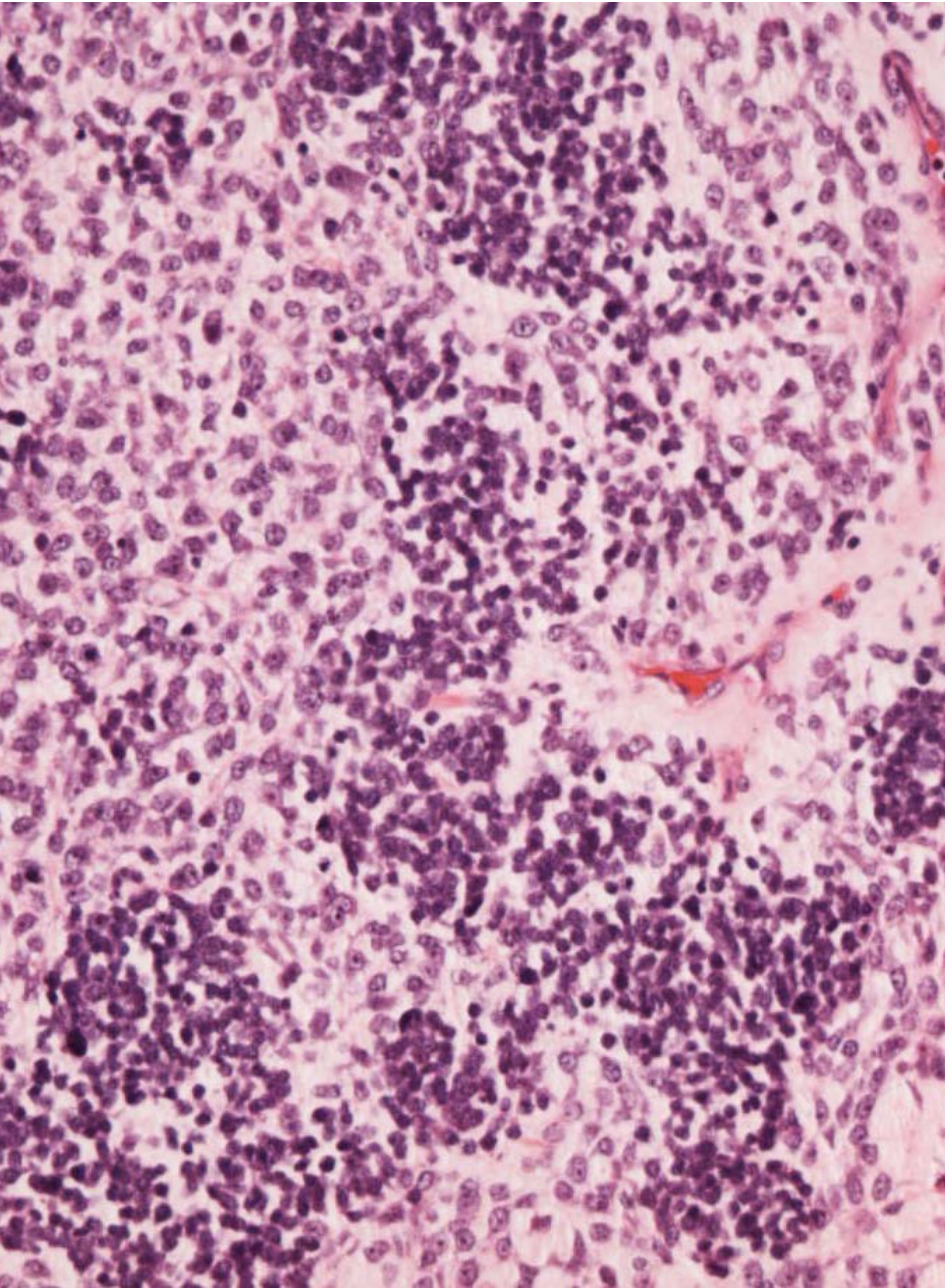
Rhabdomyosarcoma

Ewing family/Ewing-like sarcoma

Leiomyosarcoma

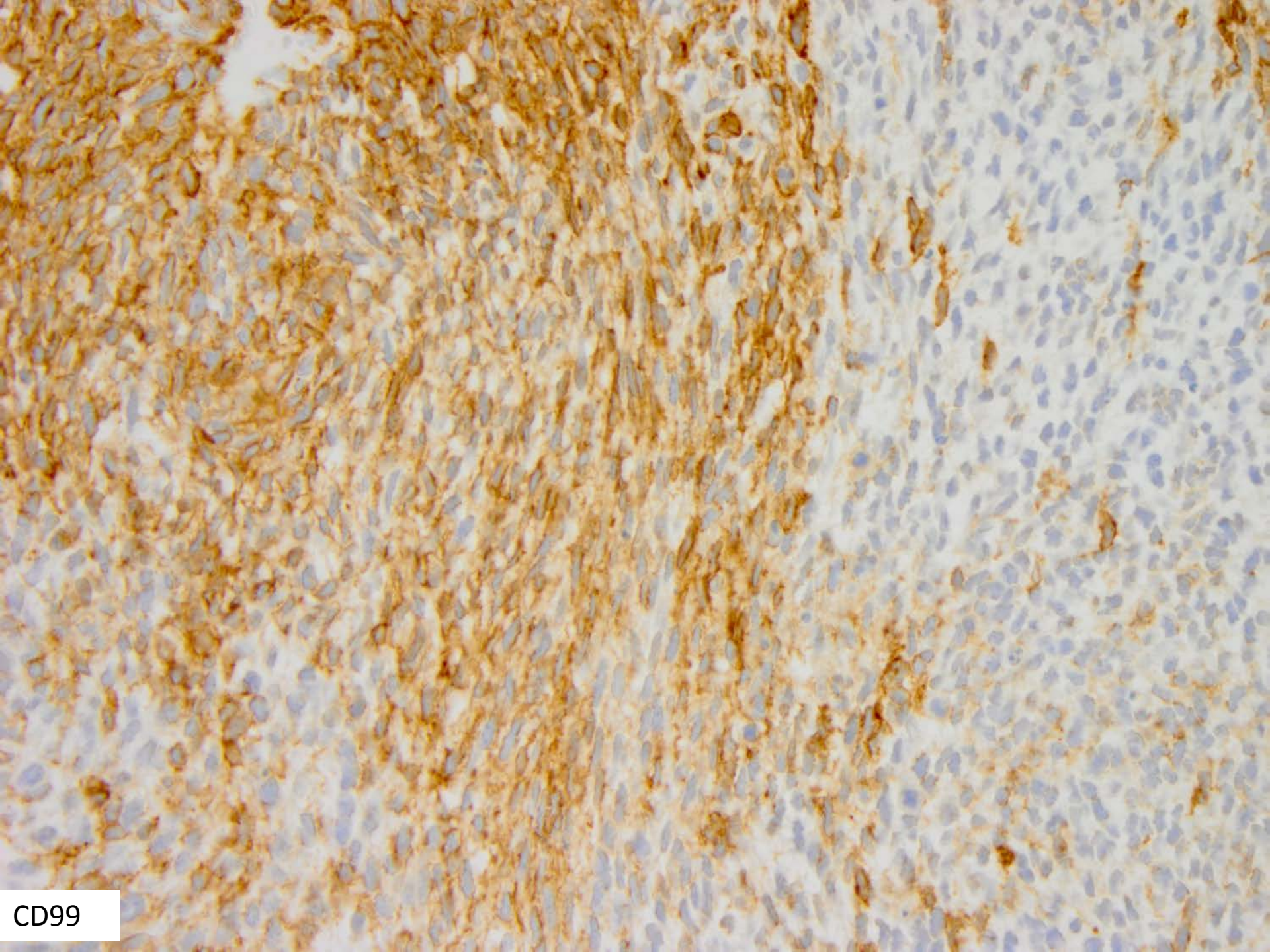
...”it resembles solid pleuropulmonary blastoma – a DICER1 associated tumor?”

Pleuropulmonary blastoma type 3 (another patient)

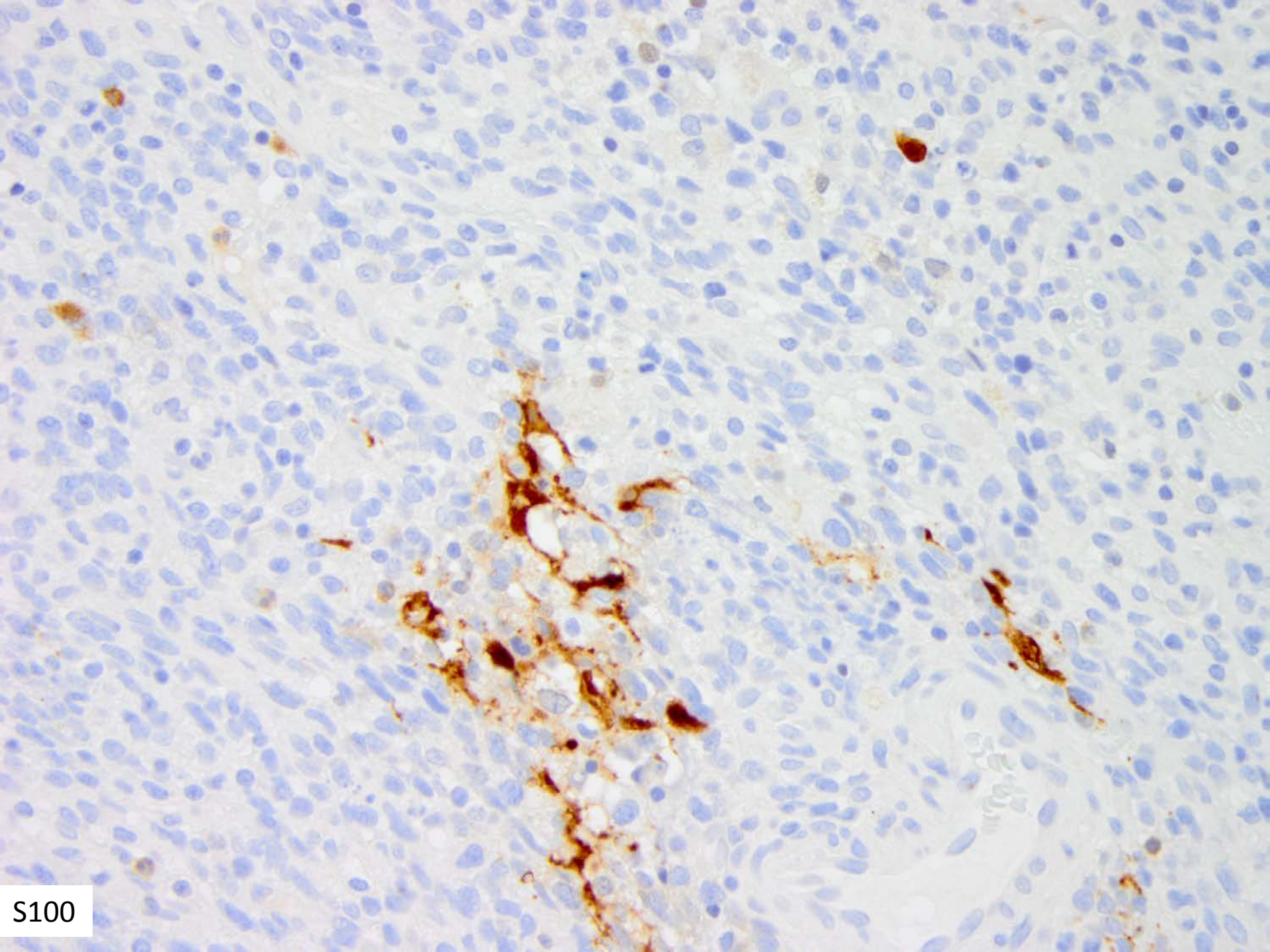


The tumor is negative for:

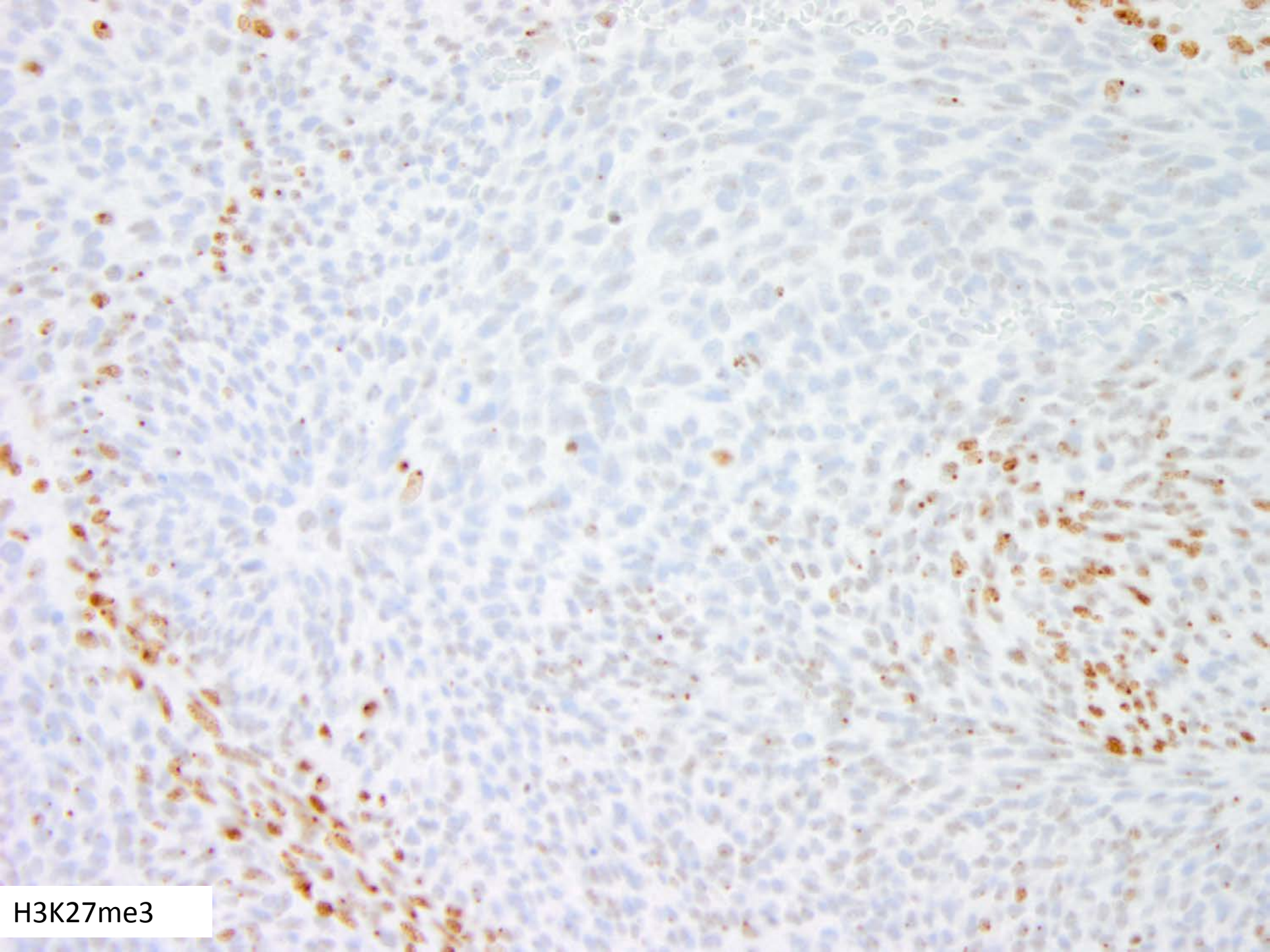
- GFAP
- OliG 2
- Synaptophysin
- SOX 2
- SOX10
- CD34
- TLE 1
- STAT 6
- MNF116
- CAM5.2
- EMA
- Somatostatin receptor 2A
- ALK1
- BRG1 (SMARCA4)
- INI1 (SMARCB1)



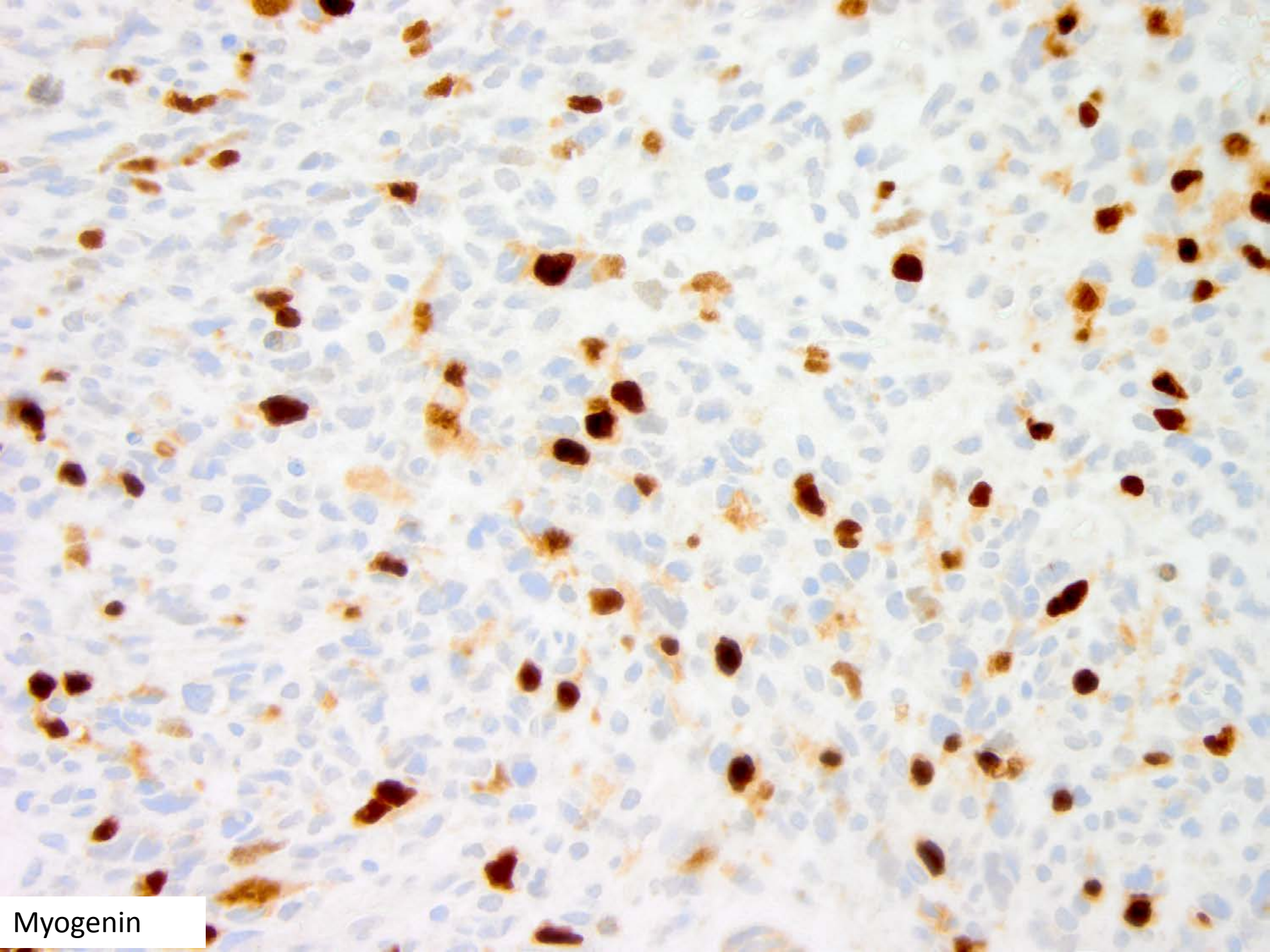
CD99



S100



H3K27me3



Myogenin

- Array CGH (not specific for a particular tumor type):
 - 103.9Mb single copy gain of 1q
 - polysomy of chromosome 2
 - 94.5 Mb single copy deletion of 6q
 - 31.8 Mb single copy 12p
- Copy number changes described in MPNST/MTT
(Brekke HR, J Clin Oncol. 2010 Mar 20;28(9):1573-82) :
 - gains of 8q, 17q, 7p, 16p
 - losses of 1p, 3p, 9p, 10q, 11q, 16q, 17p, 22q, Xp

Diagnosis:

Right temporal hemorrhagic lesion, gross total resection:

- High-grade malignant spindle cell tumor with rhabdomyosarcomatous differentiation

OncoPanel (Illumina HiSeq):

- DICER1 c.5125G>A (p.D1709N) in 43% of reads
- DICER1 c.904-1G>A () in 42% of reads
- KRAS c.35G>A (p.G12D) in 69% of reads

Note:

- DICER1 c.5125G>A (p.D1709N) :

- Hotspot variant (Brennan M et al. F1000 Research 2015, 4-217)
- Deregulates miRNA production and promotes cell growth and differentiation

- DICER1 c.904-1G>A ():

- Predicted to eliminate the acceptor site at 3' end of intron 9 and to abrogate or reduce the activity of the DICER1 protein product.

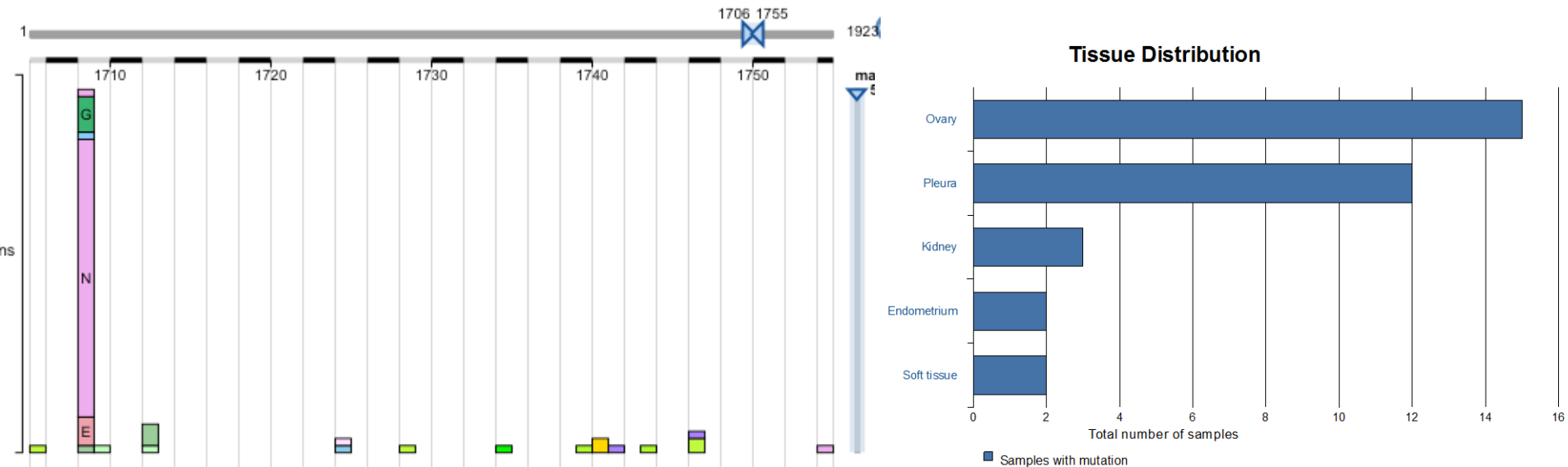
- KRAS c.35G>A (p.G12D):

- Hotspot mutation, known to be activating (Rachagani S. et al. Br J Cancer. 2011 Mar 15;104(6):1038-48)

- Diagnosis:
 - Primary CNS DICER1-associated sarcoma
- Referral for consultation with the cancer predisposition program at DFCI
- Treatment: DFCI pleuropulmonary blastoma protocol
- The child is without evidence of recurrent disease after 1 year

DICER1 Tumor predisposition syndrome

- Autosomal dominant inheritance
- Two hit mechanism in DICER1-derived tumorigenesis:
 - Frameshift or splice germline mutation
 - Missense somatic mutation



Age <6 years

Ages 6 to ~40 years

PitB
Malignant
ages <24 months
(*n*<10)

PPB
Malignant
Cystic PPB
~ ages 0–3 years
(*n*>100)

Cystic/solid
& solid PPB
~ ages 2–6 years
(*n*>200)

CN
Benign
ages 0–4 years
(*n*~45)

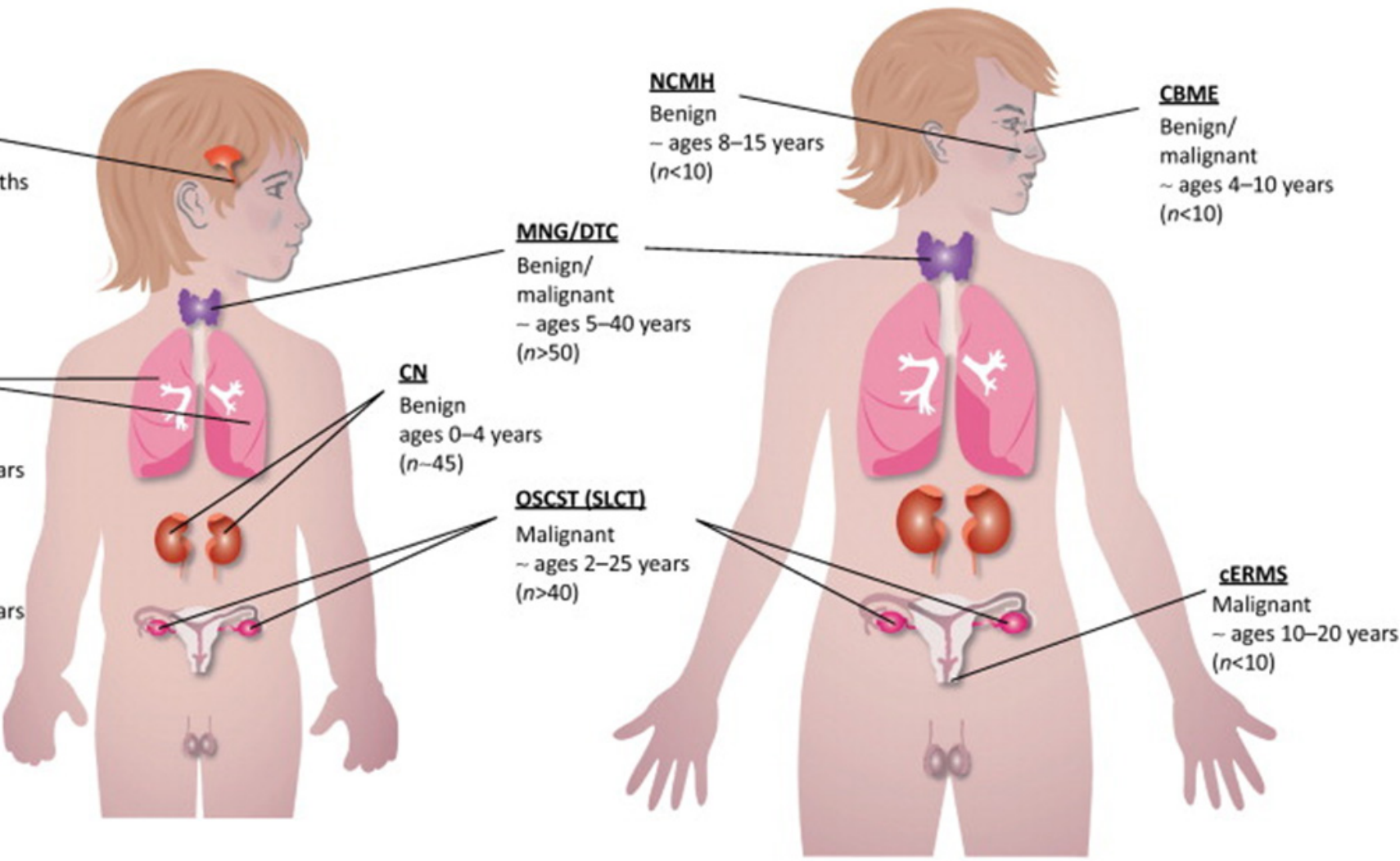
MNG/DTC
Benign/
malignant
~ ages 5–40 years
(*n*>50)

OSCST (SLCT)
Malignant
~ ages 2–25 years
(*n*>40)

NCMH
Benign
~ ages 8–15 years
(*n*<10)

CBME
Benign/
malignant
~ ages 4–10 years
(*n*<10)

cERMS
Malignant
~ ages 10–20 years
(*n*<10)



Interesting facts about this case

- Our patient does not have a DICER1 germline variant
- The pathogenic mechanism is similar to the one described in DICER1 syndrome-associated tumors
- The histology predicted the molecular results (at least for one reviewer)
- A primary intracranial DICER1 sarcoma has not been described yet
- Index case that prompted a search in our archives and identification of 12 other cases with similar histology and immunoprofile.

The image shows the exterior of the Boston Children's Hospital. The building is a multi-story structure with a brick facade. A prominent blue horizontal band runs across the middle of the building, featuring the hospital's logo on the left and the text "Boston Children's Hospital" in white, sans-serif font. Above this band, three colorful banners are hanging from the building. The banners are: a blue and green geometric pattern, a yellow banner with a row of red triangles, and a blue banner with a red circle and a white cross. In the foreground, several large, cylindrical columns are visible, each decorated with horizontal bands of different colors: orange, pink, brown, blue, and teal. The sky is overcast and grey.

 Boston Children's Hospital

Thank you