AANP Diagnostic Slide Session 2022 Case #3

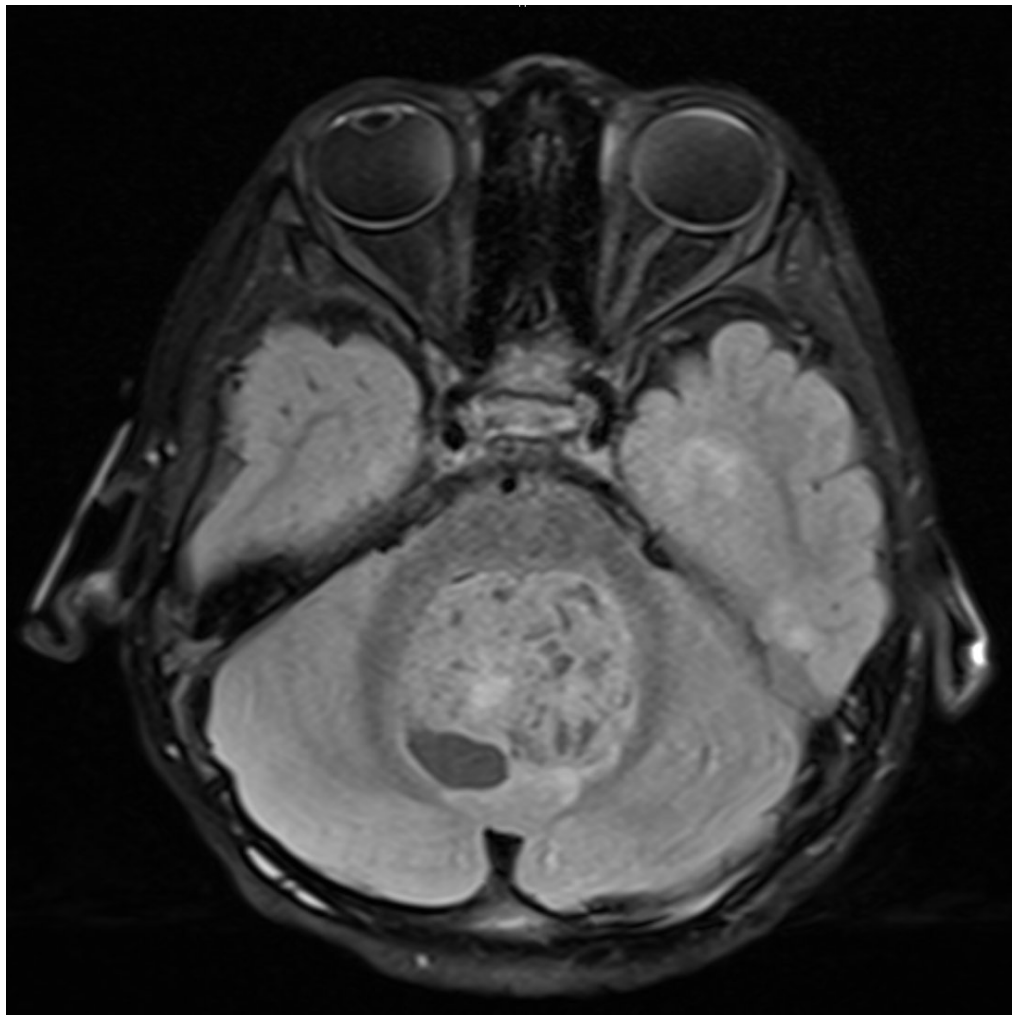
Melanie Lang-Orsini, MB, BCh, BAO[1], Viharkumar Patel, MD[2], Kenneth Aldape, MD[3], Jessica Clymer, MD[4], Edward Smith, MD[5], Anat Stemmer-Rachamimov, MD[1], Sanda Alexandrescu, MD[2]

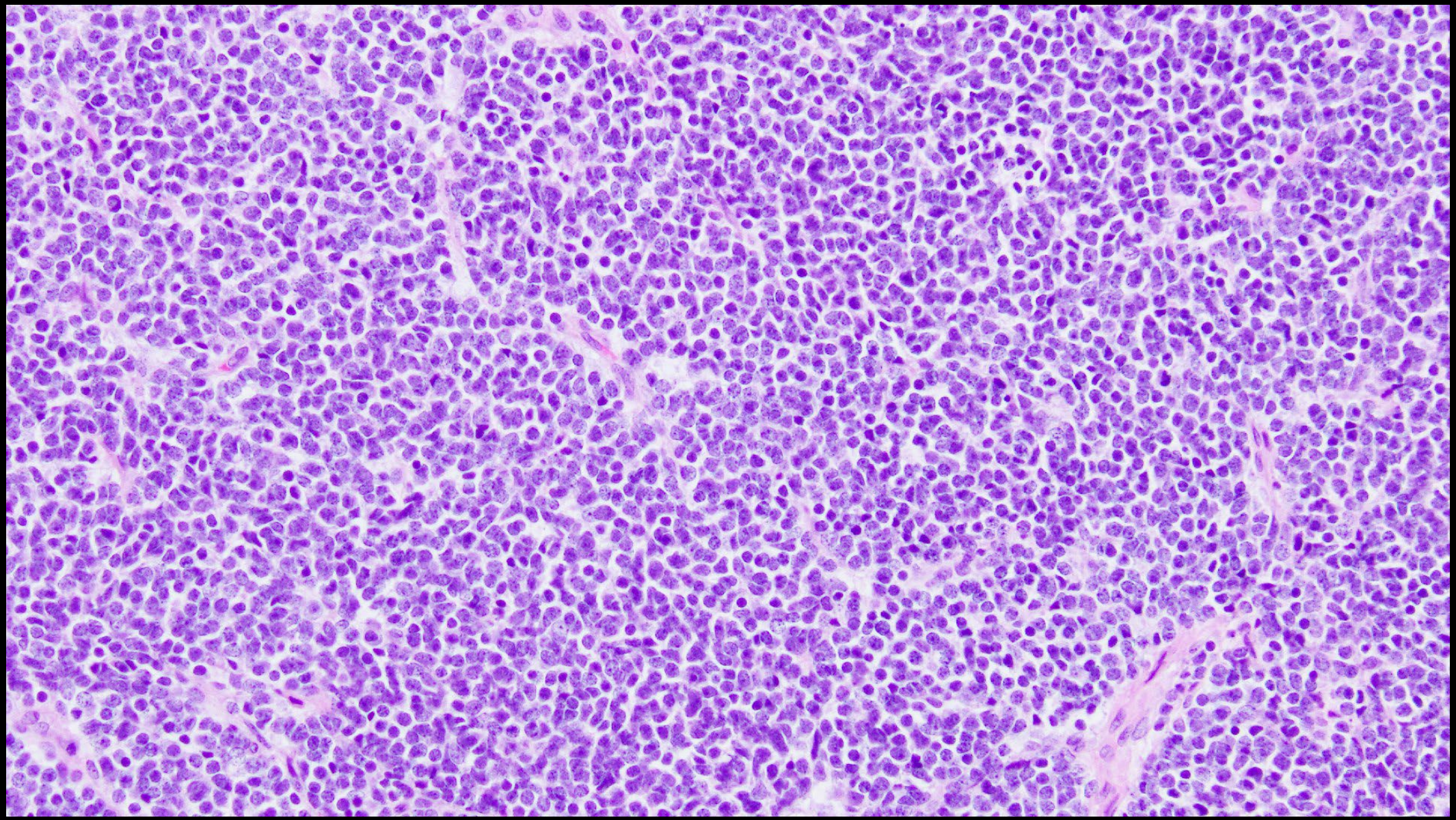
1. Department of Pathology, Massachusetts General Hospital, Harvard Medical School; 2. Department of Pathology, Boston Children's Hospital, Harvard Medical School; 3. Center for Cancer Research, National Institute of Health; 4. Department of Pediatric Oncology, Boston Children's Hospital, Harvard Medical School; 5. Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School

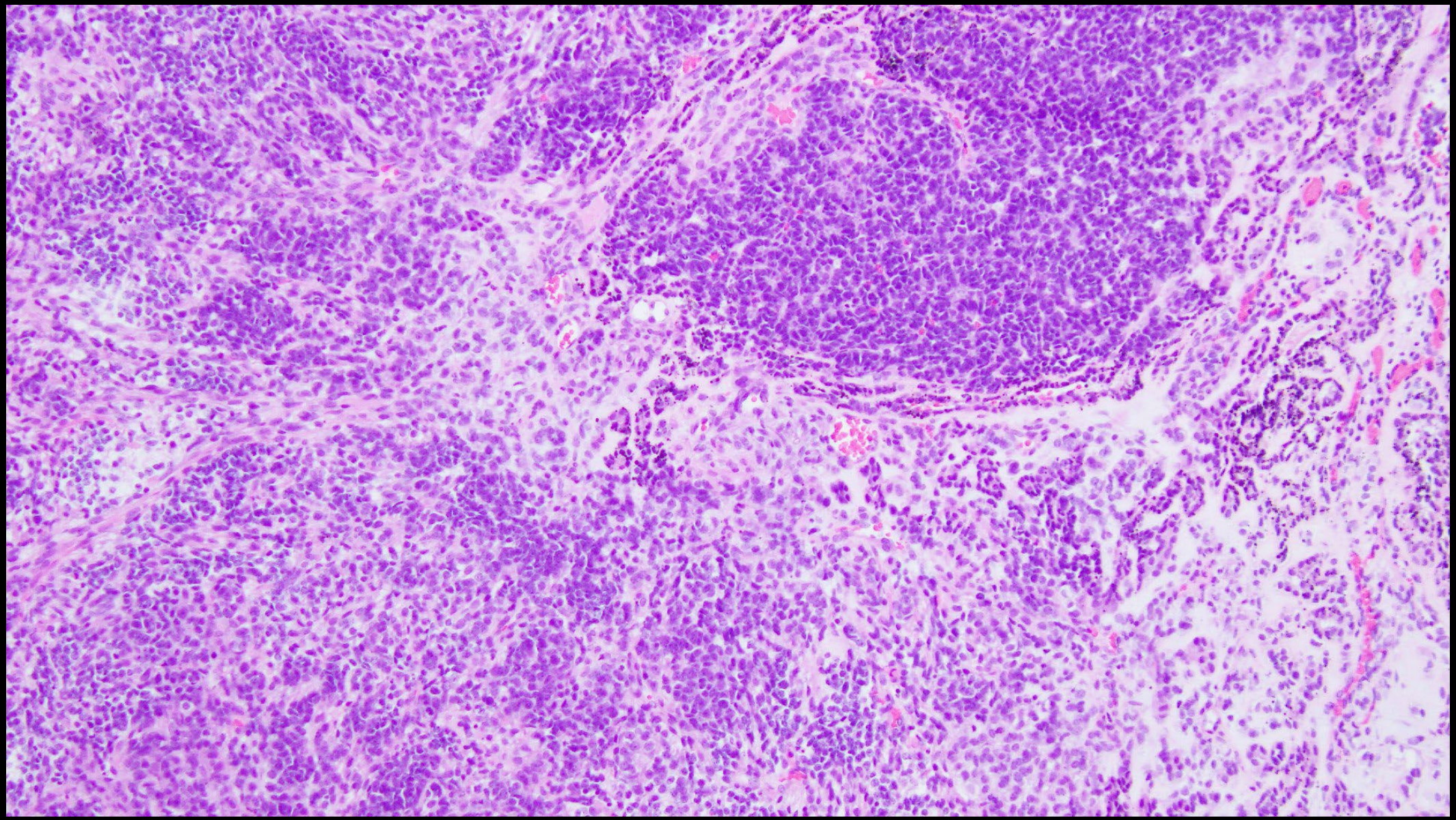
No disclosures or conflicts of interest

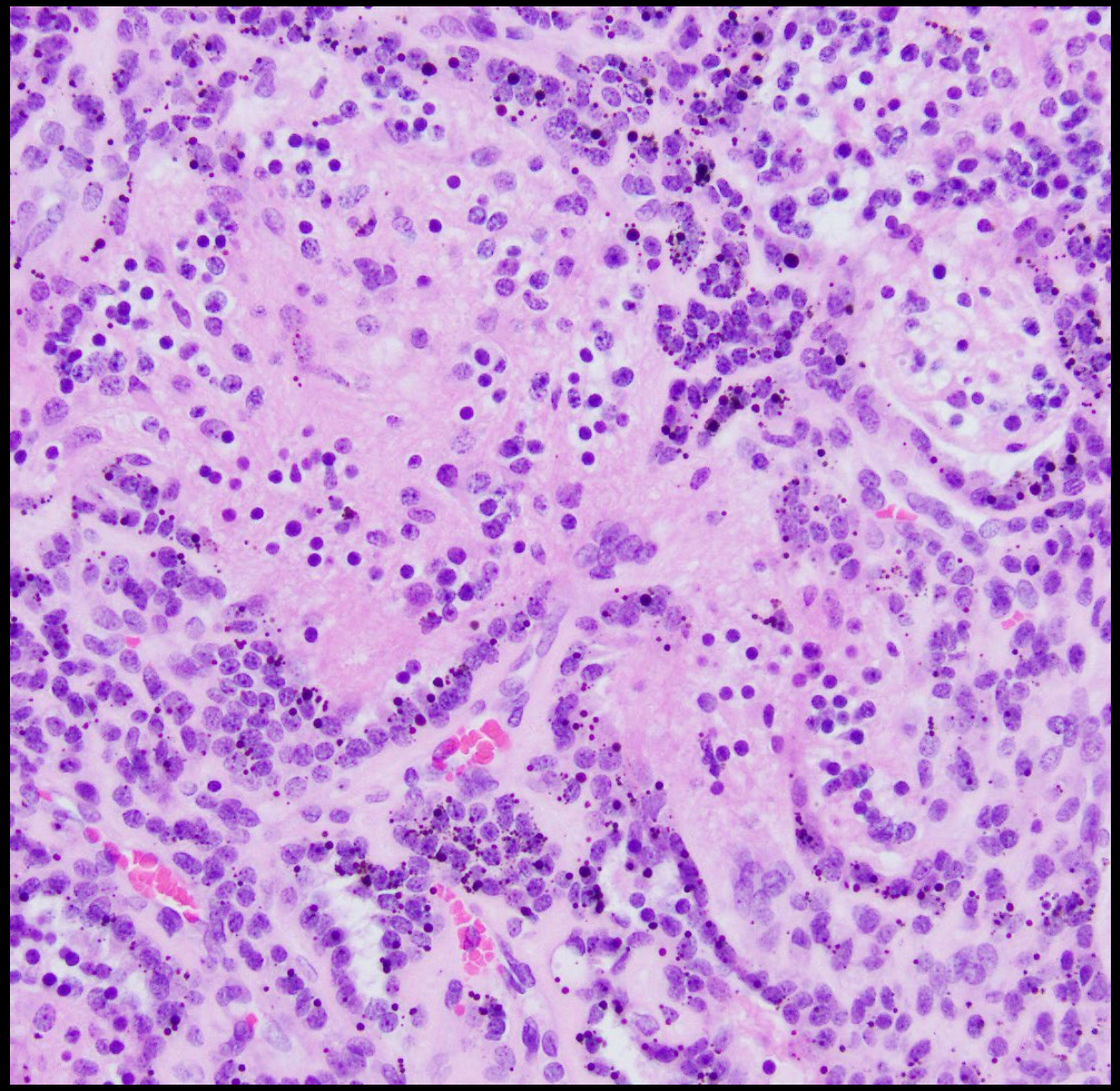
Clinical Summary

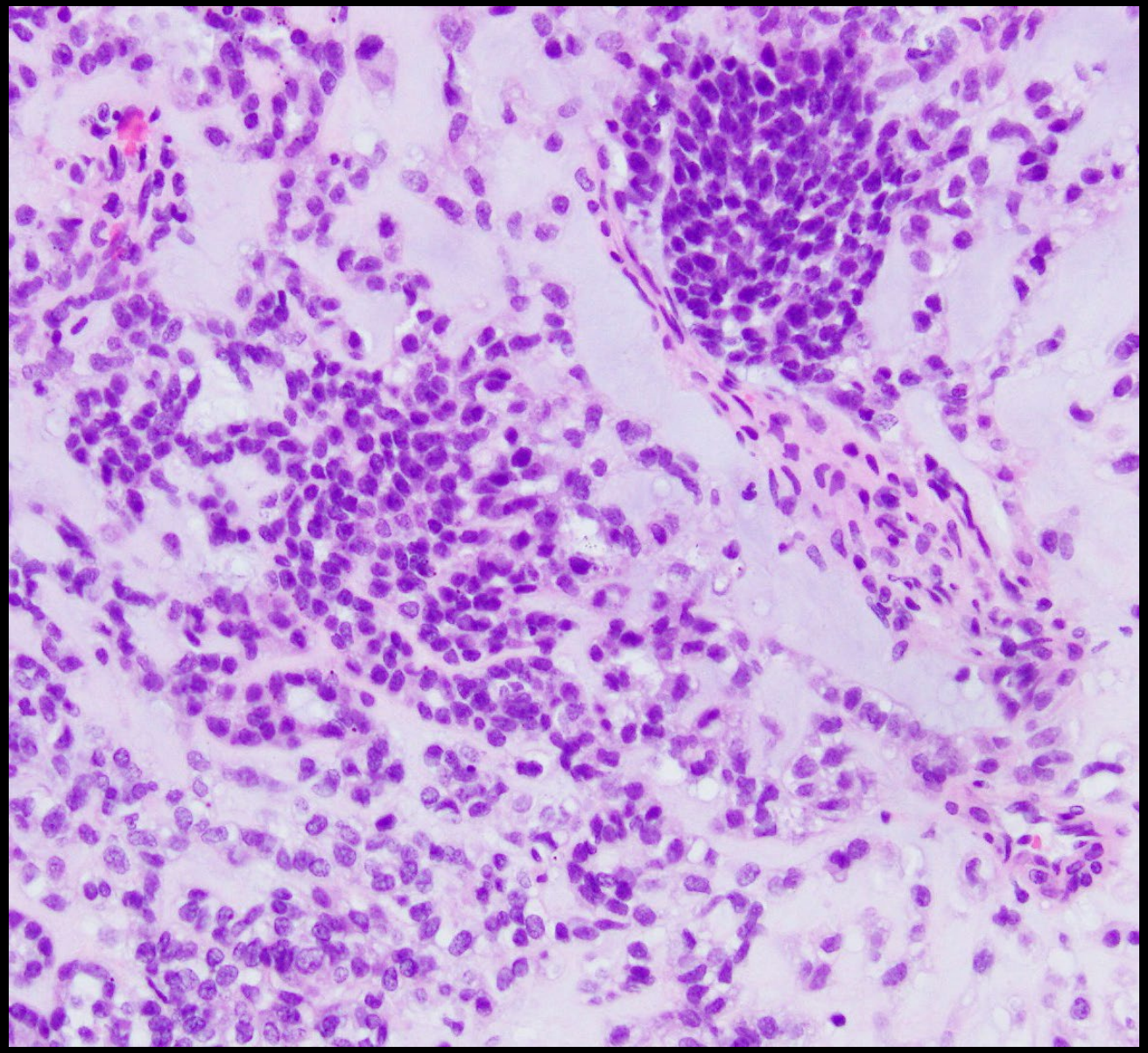
Previously healthy 2-year-old boy presented with several weeks of worsening headache and clumsiness, then in the ER with acute profound deterioration with nausea and vomiting

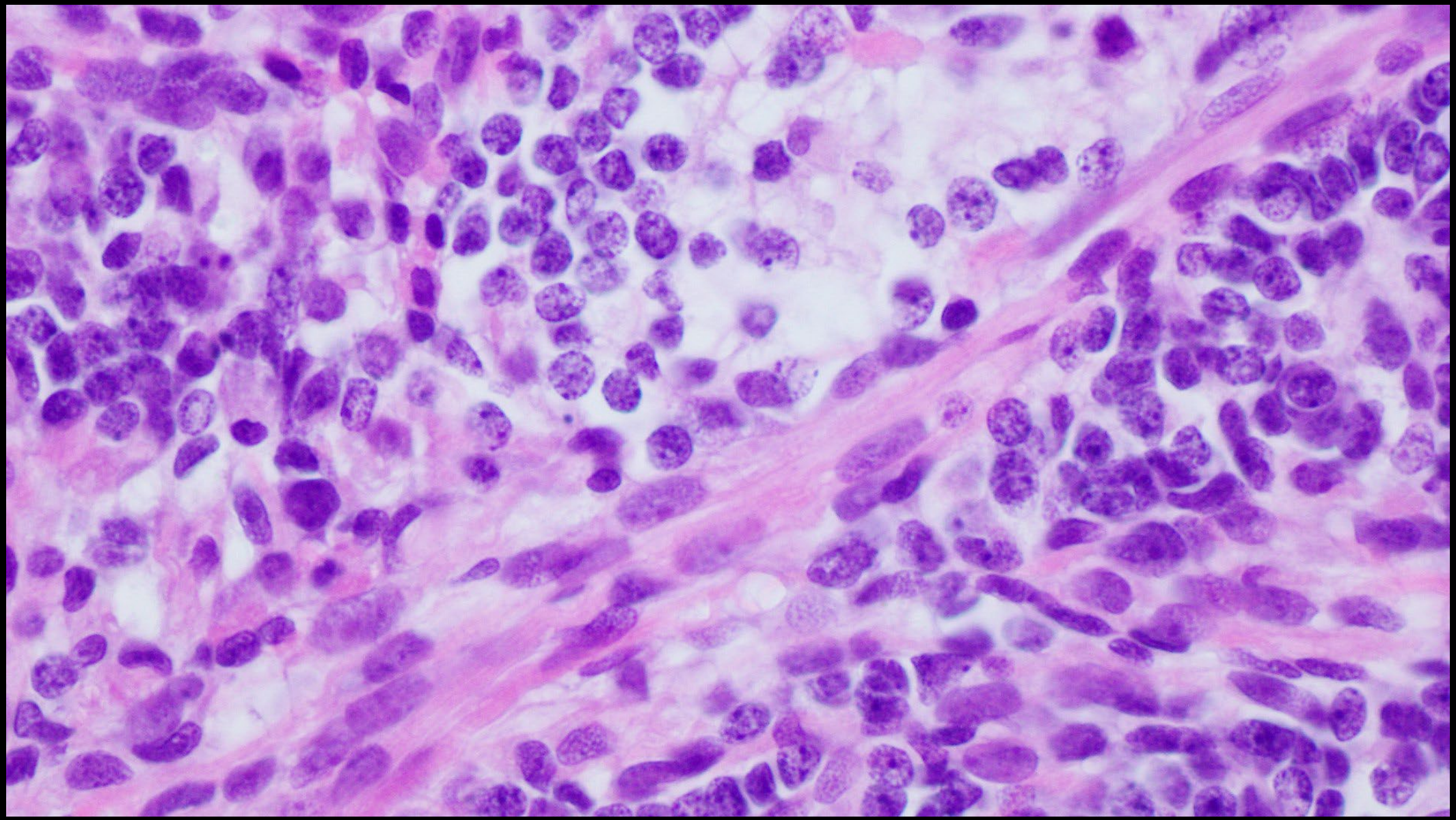








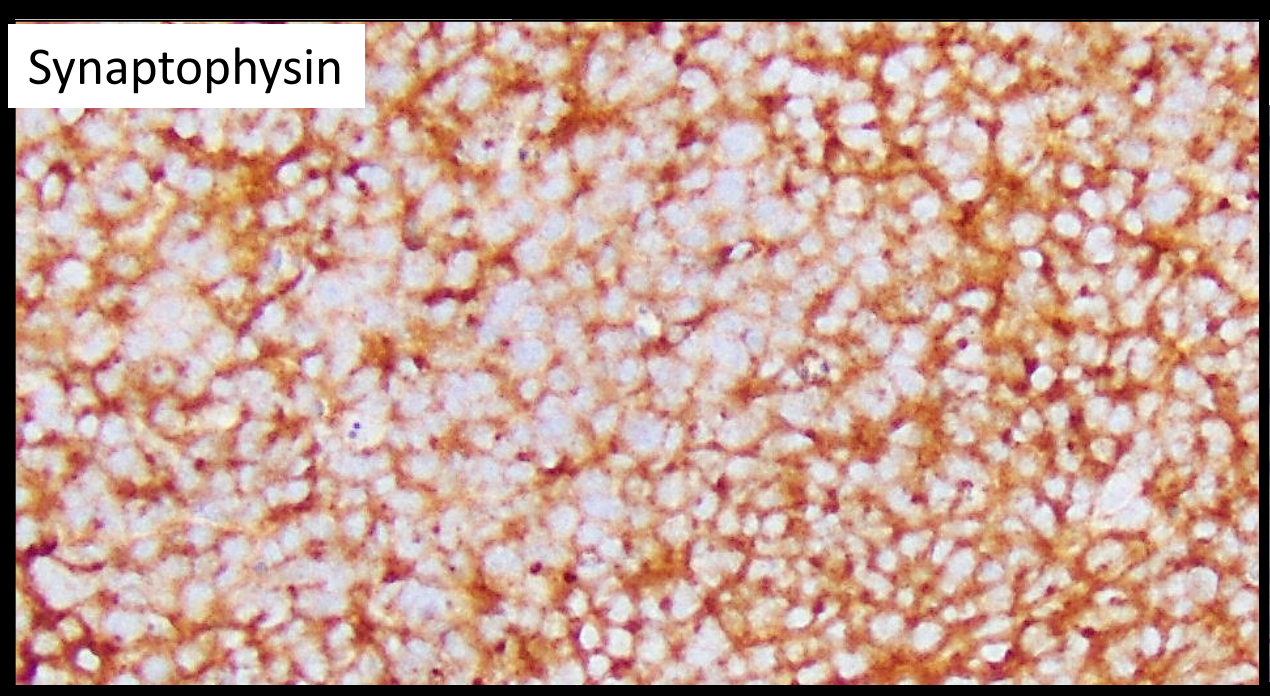


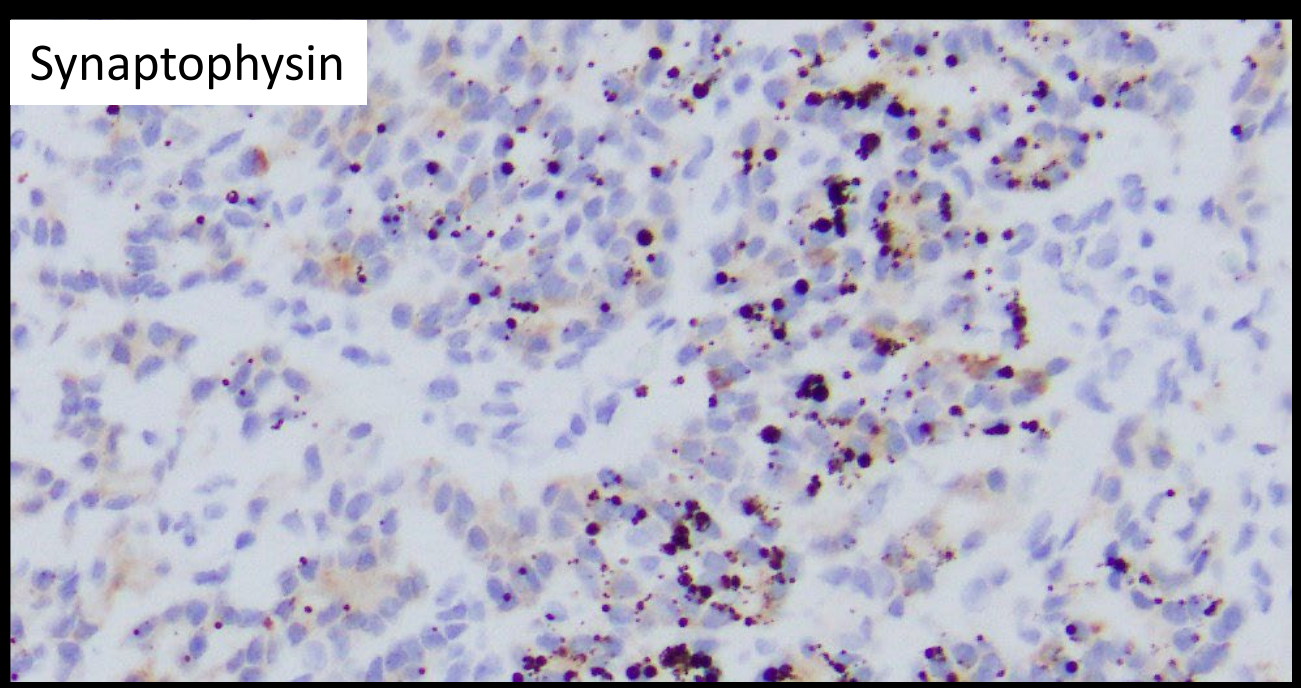


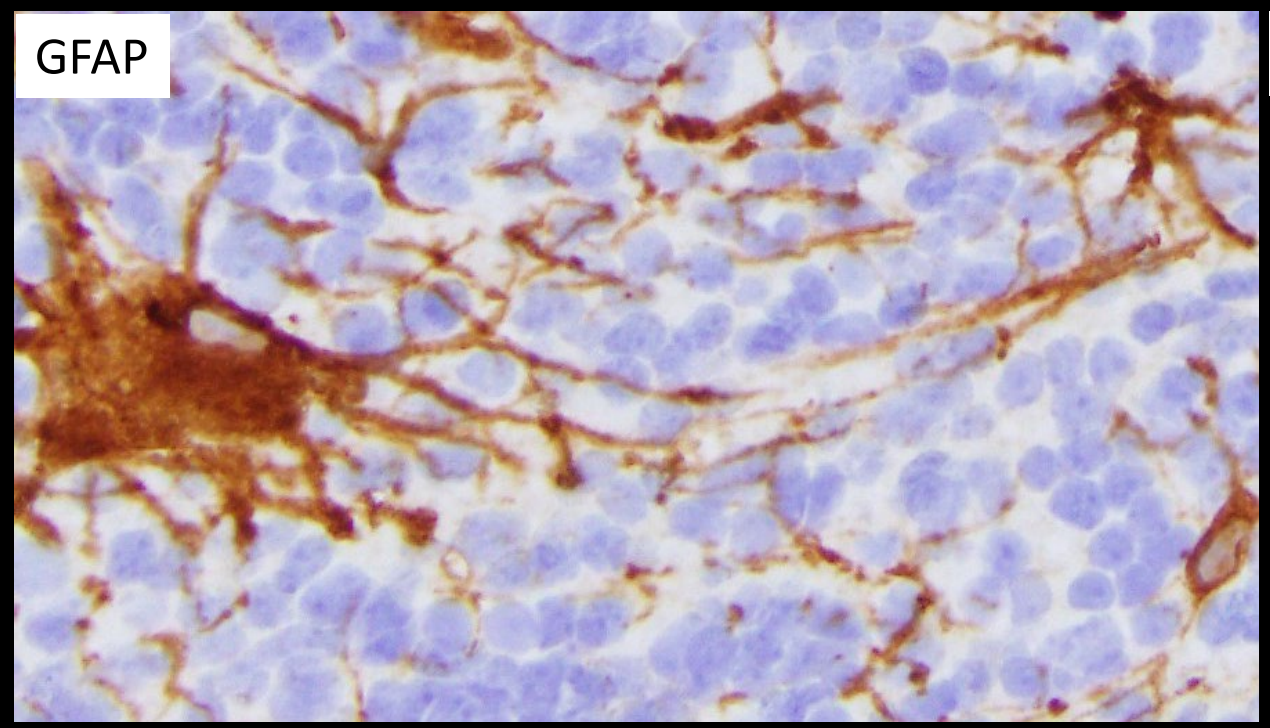
Differential diagnosis?

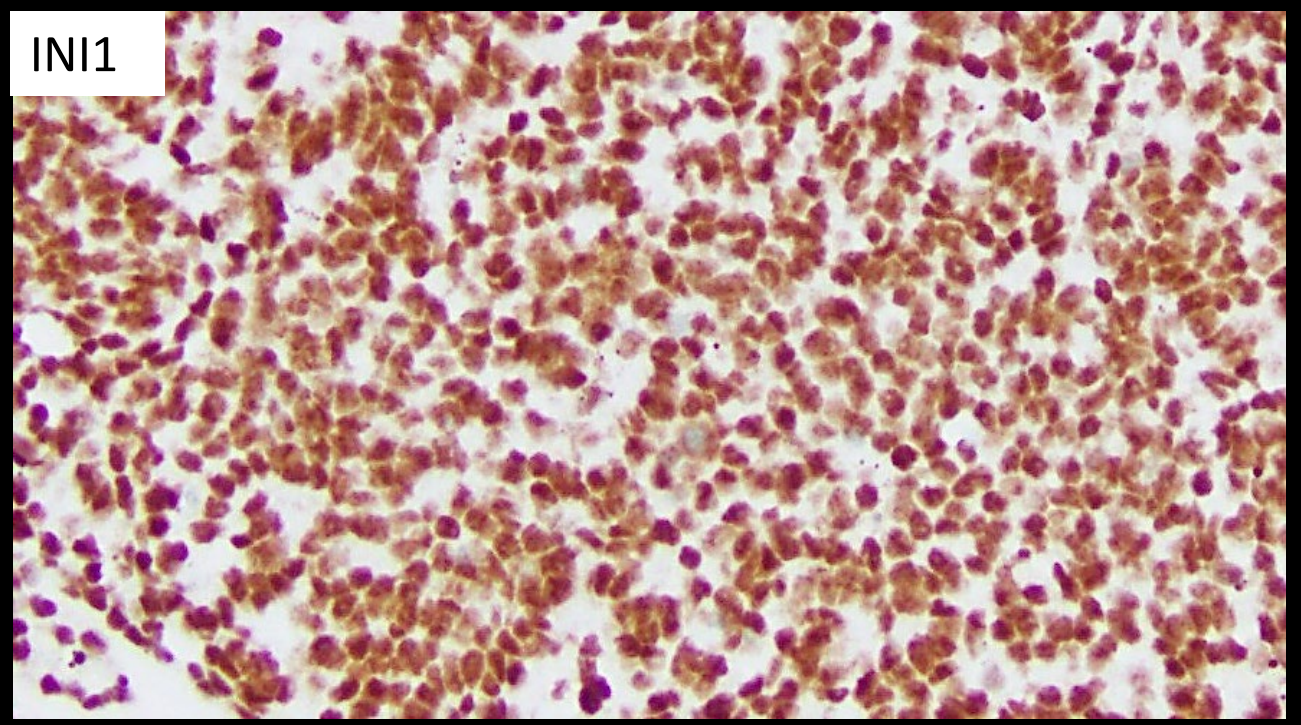
Differential Diagnosis

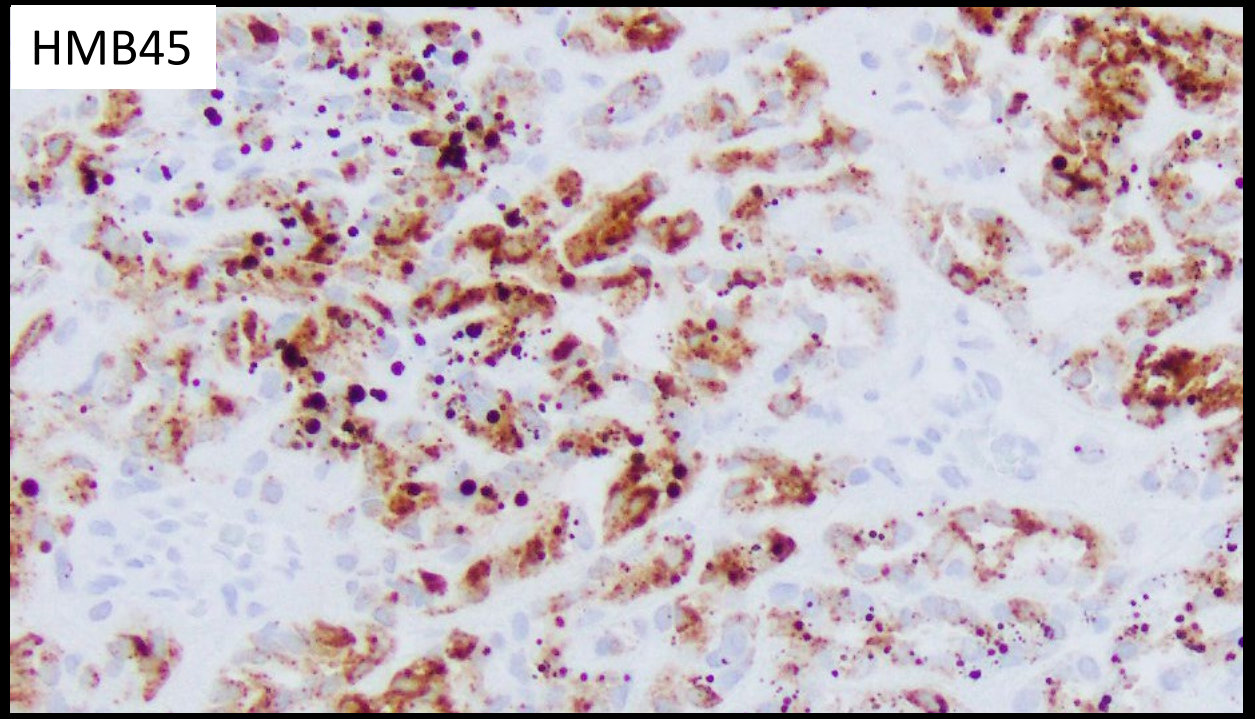
Differential Diagnosis	Supporting features
Pineal anlage tumor	Pigmented epithelium and striated muscle, **but no connection to pineal gland on MRI**
ETMR-like DICER1-associated tumor	Embryonal tumor with heterologous elements in the posterior fossa
Immature teratoma with embryonal tumor-like elements	Neuroectodermal and mesenchymal elements, **but no endoderm-derived elements in specimen received**
Medulloblastoma with myogenic and melanocytic differentiation	Posterior fossa location, embryonal tumor areas, evidence of myogenic and melanocytic differentiation
AT/RT	Embryonal tumor areas, mesenchymal areas, epithelial areas

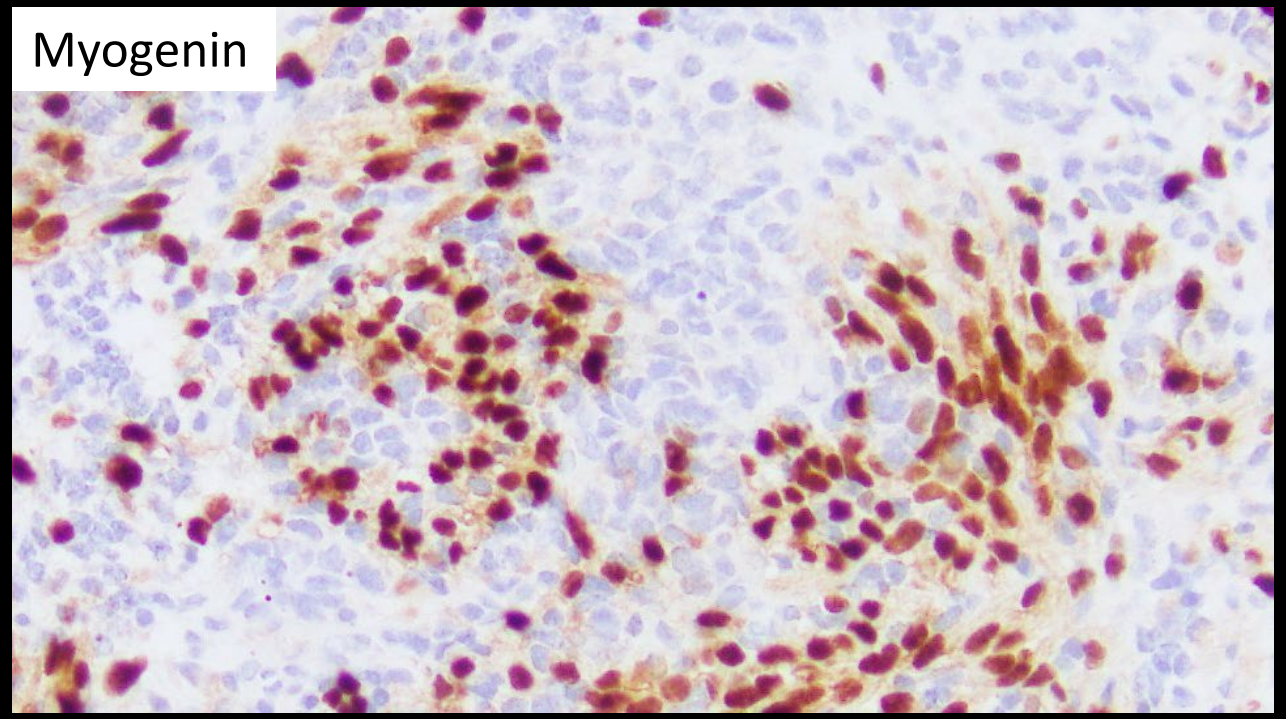

Synaptophysin

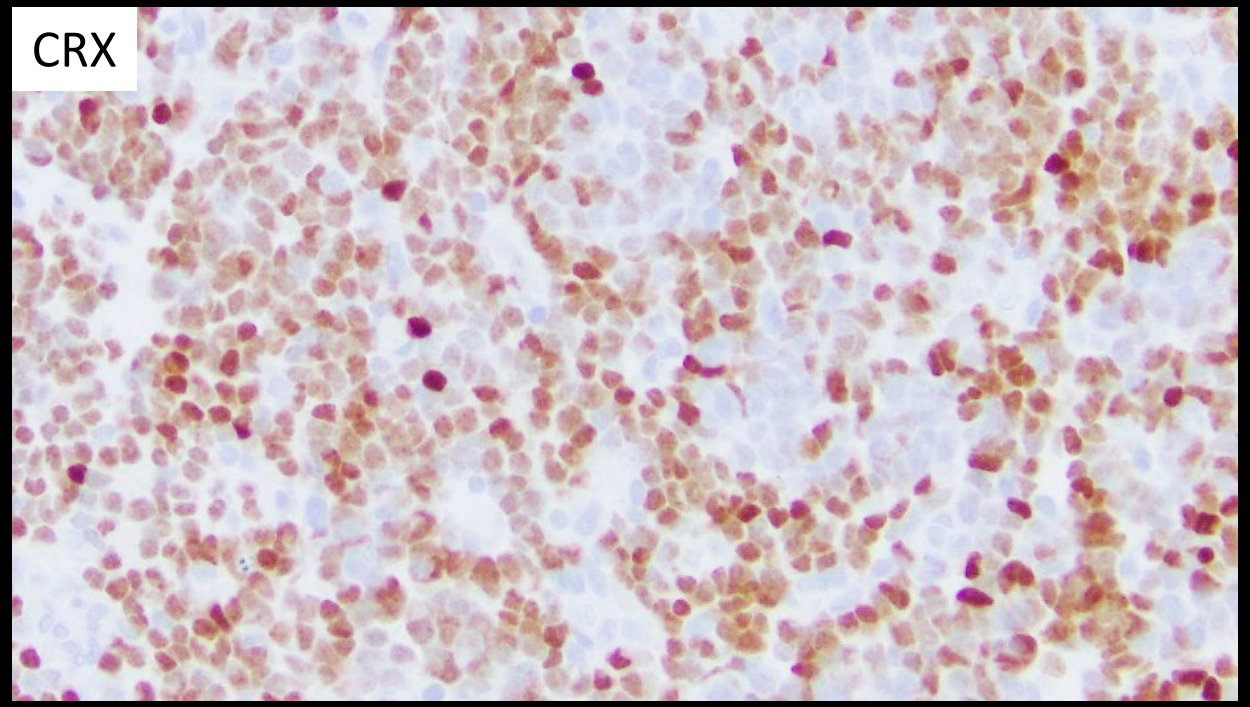

Synaptophysin

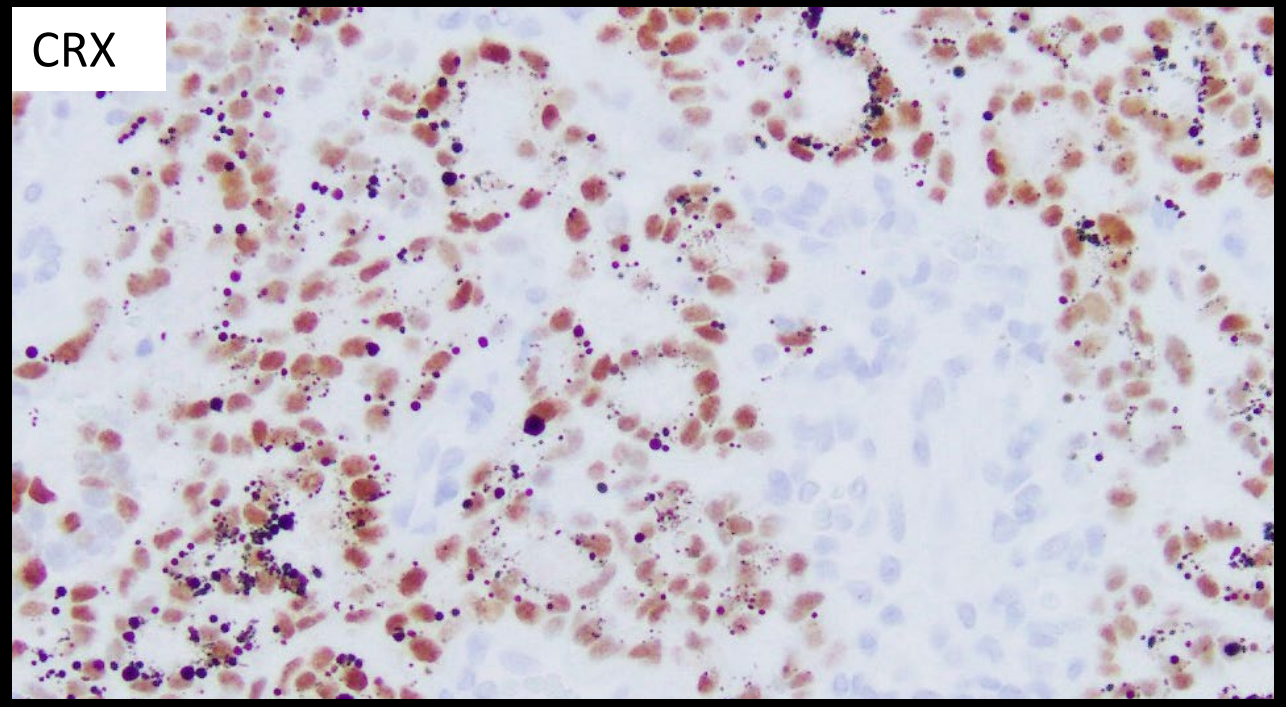

GFAP


INI1


HMB45


Myogenin

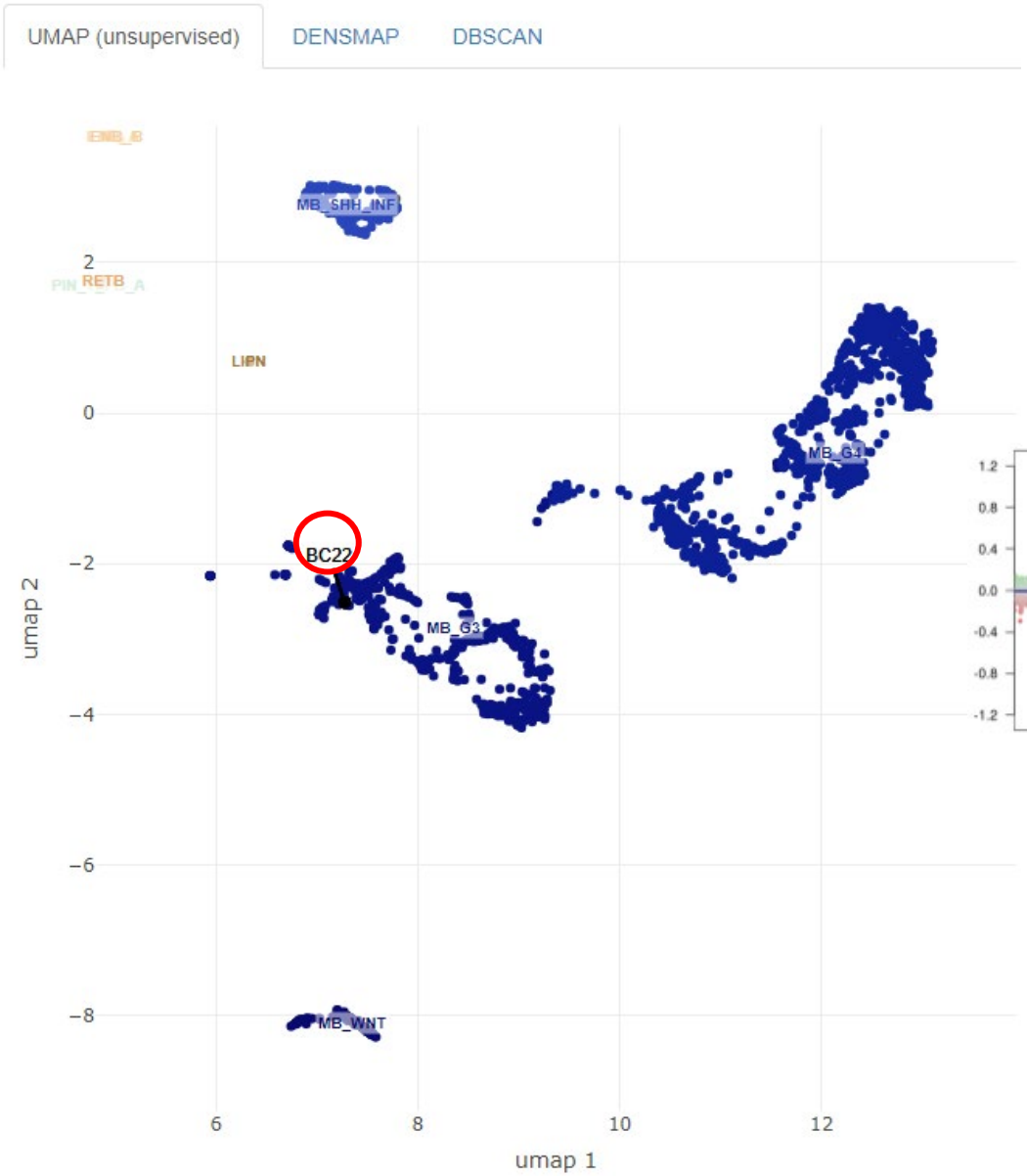

CRX

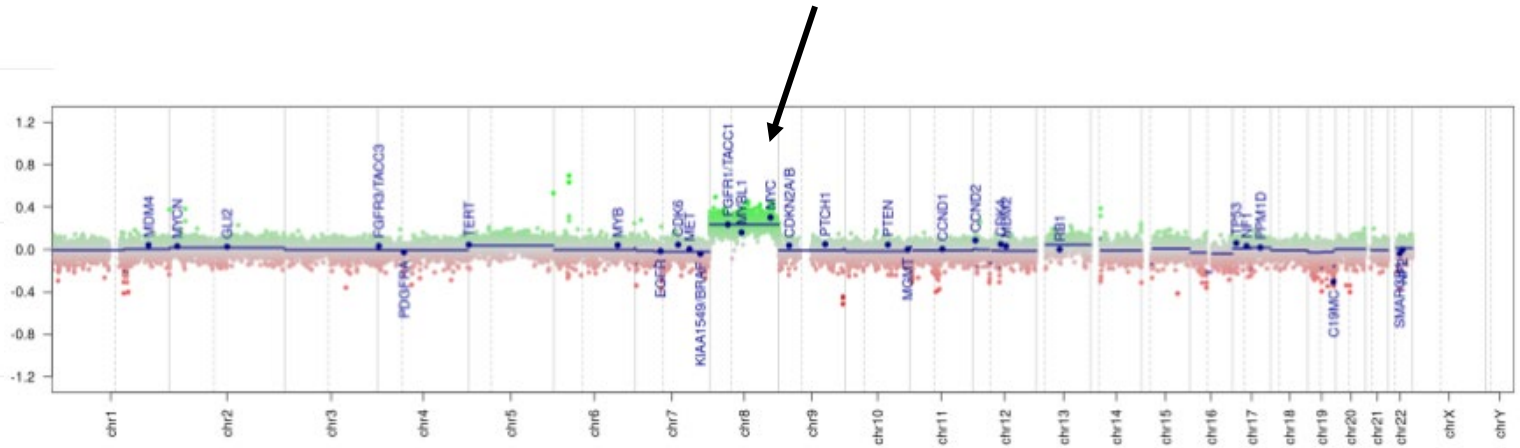

CRX

Molecular Characterization

- Oncopanel Illumina HiSeq2500: no mutations
  - No *DICER1* mutations
  - No mutations characteristic for medulloblastoma
- Copy number analysis: polysomy 8 and 1-2 copy loss of *TSC1* at 9q
- Array CGH: confirmed polysomy 8, no additional aberrations
  - No C19MC amplification
- Pediatric solid tumor & brain tumor fusion panel: negative

Methylation Profiling





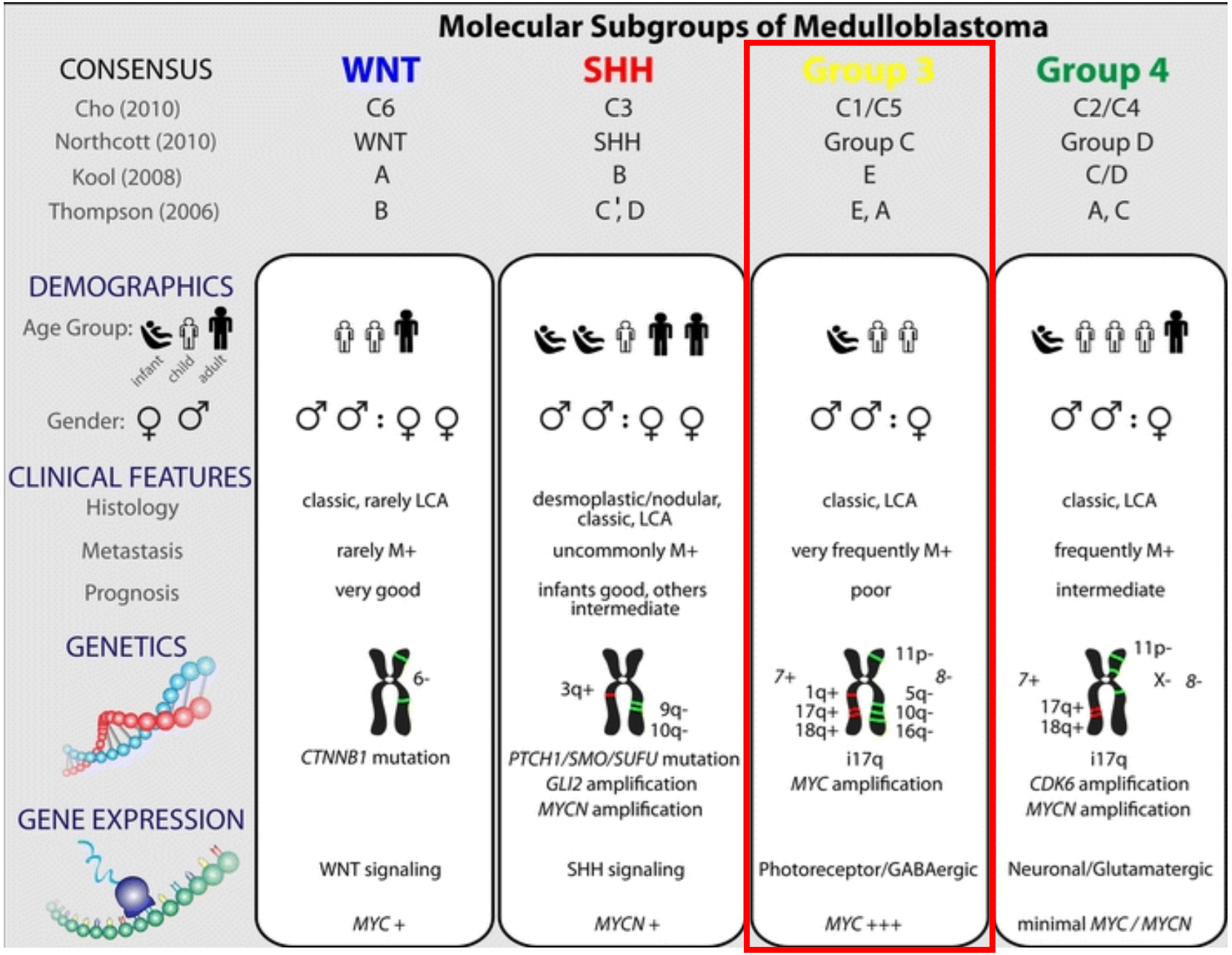
Calibrated score: 0.98

Integrated Diagnosis

Medulloblastoma with myogenic and melanocytic differentiation, molecular group 3, WHO grade 4

Brief Discussion

- Medulloblastoma: cerebellar embryonal tumor
- Second most common malignant CNS tumor in childhood
- Considerable biologic heterogeneity
  - Molecular and histologic subtypes
- **Both melanotic and myogenic differentiation have been described in medulloblastoma, but these patterns are rare, and their occurrence together even more so**



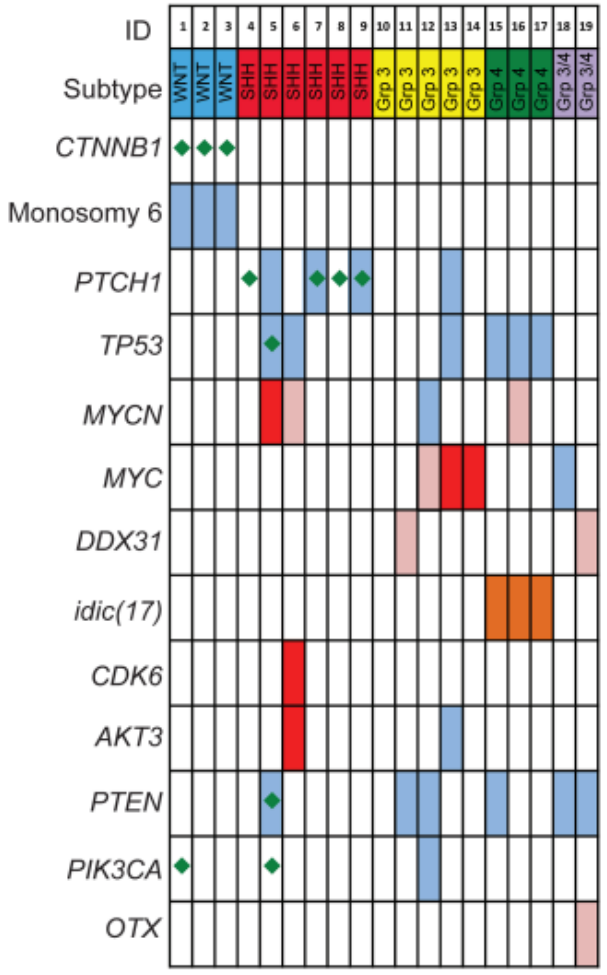
Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012 Apr;123(4):465-72.

Neuro-Oncology
19(7), 986–996, 2017 | doi:10.1093/neuonc/now294 | Advance Access date 19 January 2017

Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors

Shakti H. Ramkissoon,* Pratiti Bandopadhayay,* Jaeho Hwang,* Lori A. Ramkissoon,* Noah F. Greenwald, Steven E. Schumacher, Ryan O'Rourke, Nathan Pinches, Patricia Ho, Hayley Malkin, Claire Sinai, Mariella Filbin, Ashley Plant, Wenya Linda Bi, Michael S. Chang, Edward Yang, Karen D. Wright, Peter E. Manley, Matthew Ducar, Sanda Alexandrescu, Hart Lidov, Ivana Delalle, Liliana C. Goumnerova, Alanna J. Church, Katherine A. Janeway, Marian H. Harris, Laura E. MacConaill, Rebecca D. Folkerth, Neal I. Lindeman, Charles D. Stiles, Mark W. Kieran, Azra H. Ligon, Sandro Santagata, Adrian M. Dubuc, Susan N. Chi,§ Rameen Beroukhim,§ and Keith L. Ligon§

Targeted exome sequencing combined with genome-wide copy number profiling identified subgroup-specific genomic alterations in 90% of medulloblastomas



ID	Genetic Subgroup	Rationale
1	WNT	Monosomy 6 and *CTNNB1* mutation
2	WNT	Monosomy 6 and *CTNNB1* mutation
3	WNT	Monosomy 6 and *CTNNB1* mutation
4	SHH	*PTCH1* mutation
5	SHH	9p gain/9q loss, 17p loss, *TP53* mutation, *MYCN* amp
6	SHH	Chromothripsis, *TP53* loss, poly 2, *MYCN* amp (subclonal)
7	SHH	*PTCH1* mutation, 9p gain/9q loss
8	SHH	*PTCH1* mutation
9	SHH	*PTCH1* mutation, 9q loss, poly 2, 1q gain
10	3	Mono 2, 3 10, 11, and evidence of *GFI1B* rearrangement
11	3	Multiple Group 3 enriched polysomies, *DDX31* alteration
12	3	*MYC* amp (subclonal), Multiple Group 3 enriched polysomies
13	3	*MYC* amp, 17p loss, poly 7, 9q loss
14	3	*MYC* amp, poly 7, poly 5, poly 14
15	4	iso(17) and absence of group 3 alterations
16	4	iso(17), poly 4, *MYCN* amp (subclonal)
17	4	iso(17), *SNCAIP* dup, monosomy X, poly 7
18	3 or 4	Poly 7, poly 14, 16q loss
19	3 or 4	Poly 7, mono 8, numerous other broad changes, *OTX2* gain, *DDX31 gain*

Summary

- We present a medulloblastoma with unusual histology and molecular profile
  - Presence of both myogenic and melanocytic differentiation
  - Lack of classic mutations and copy number variants
  - Methylation profile of medulloblastoma, group 3