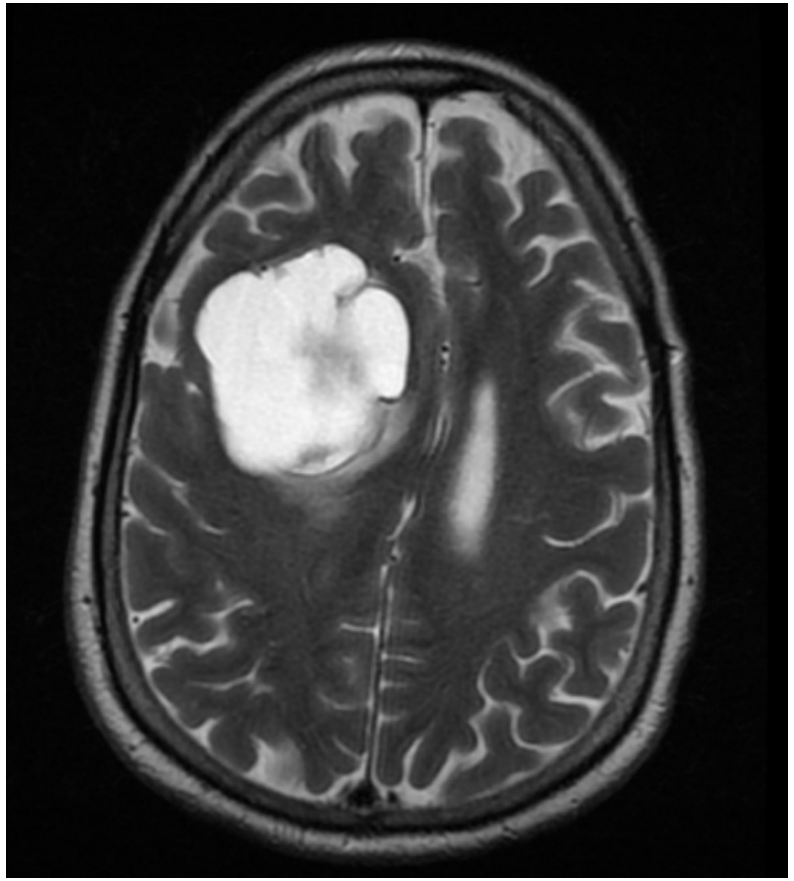
Diagnostic Slide Session 2023 Case 9

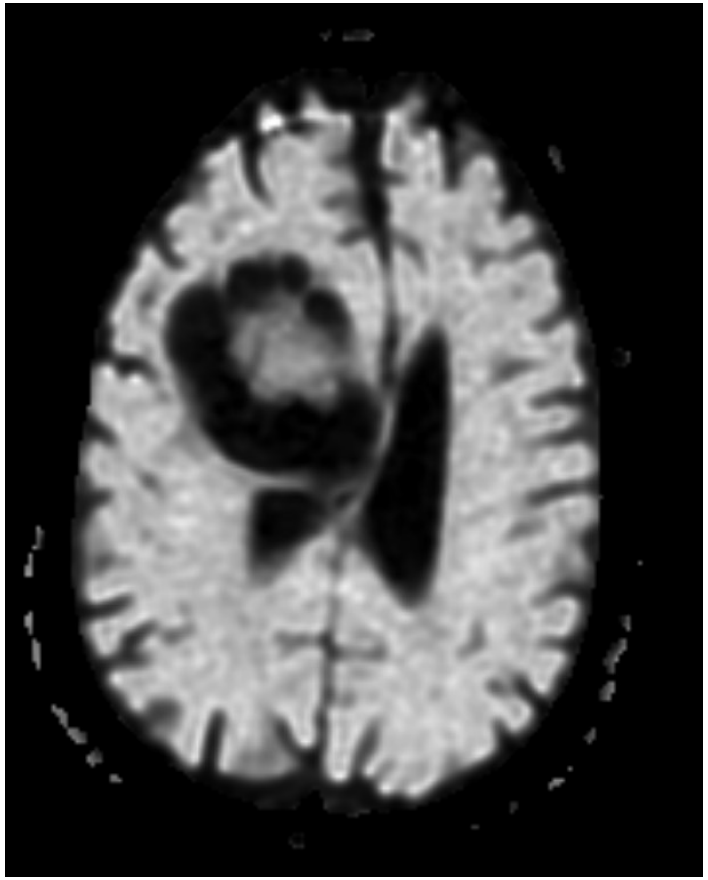
Janna Shold, DO, PGY4 and Nelli Lakis, MD, MSc
The University of Kansas Medical Center
3901 Rainbow Blvd.
Kansas City, KS 66160

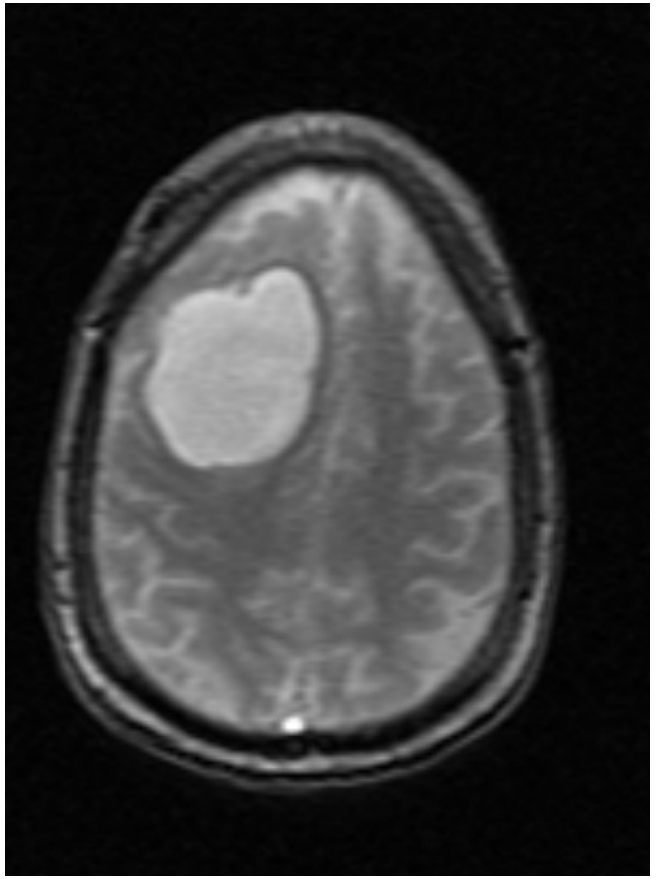
Clinical History

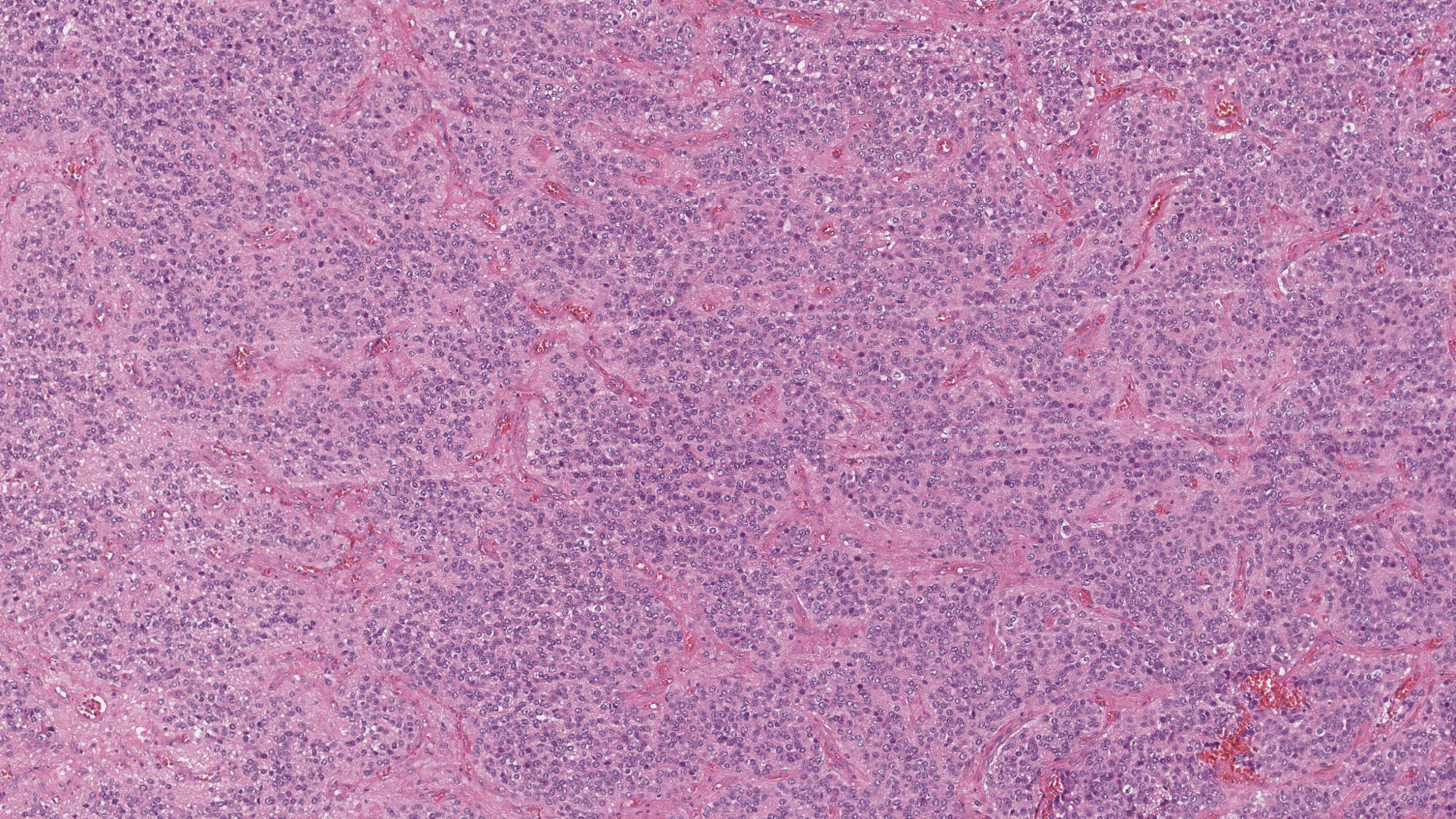
- 62-year-old male with a history of mild Hemophilia A who presents with recurrent episodes of syncope

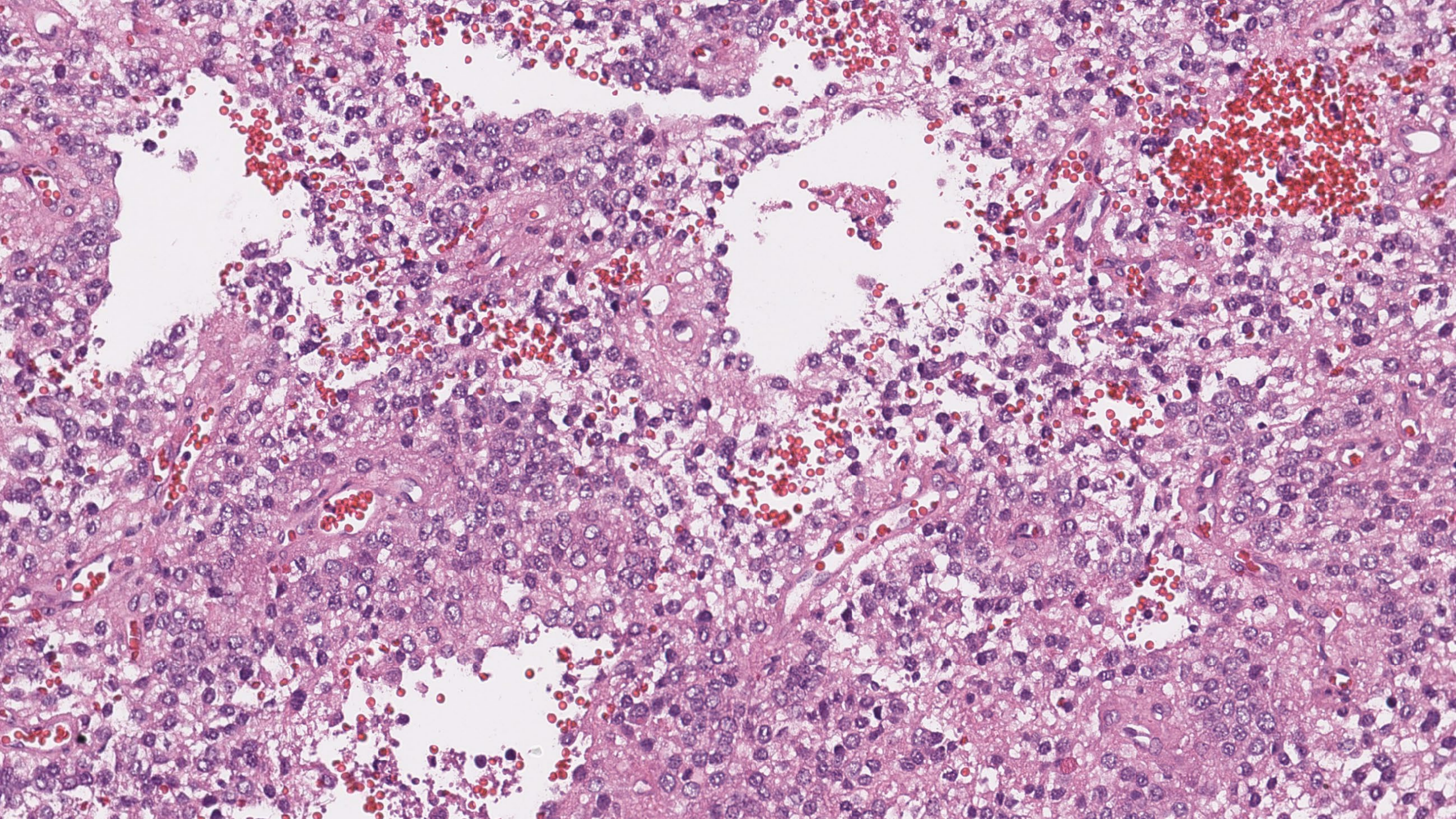
Imaging

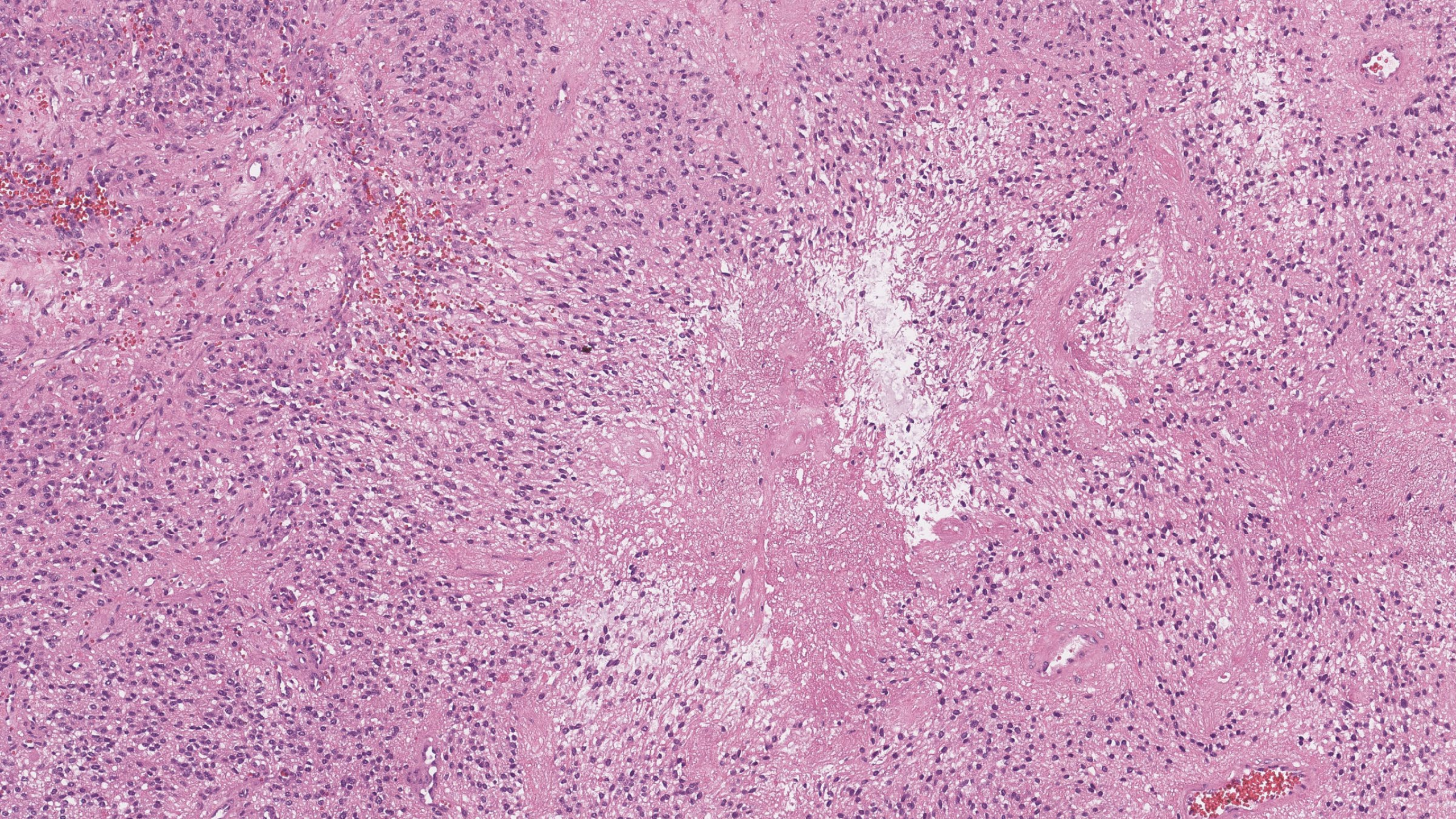


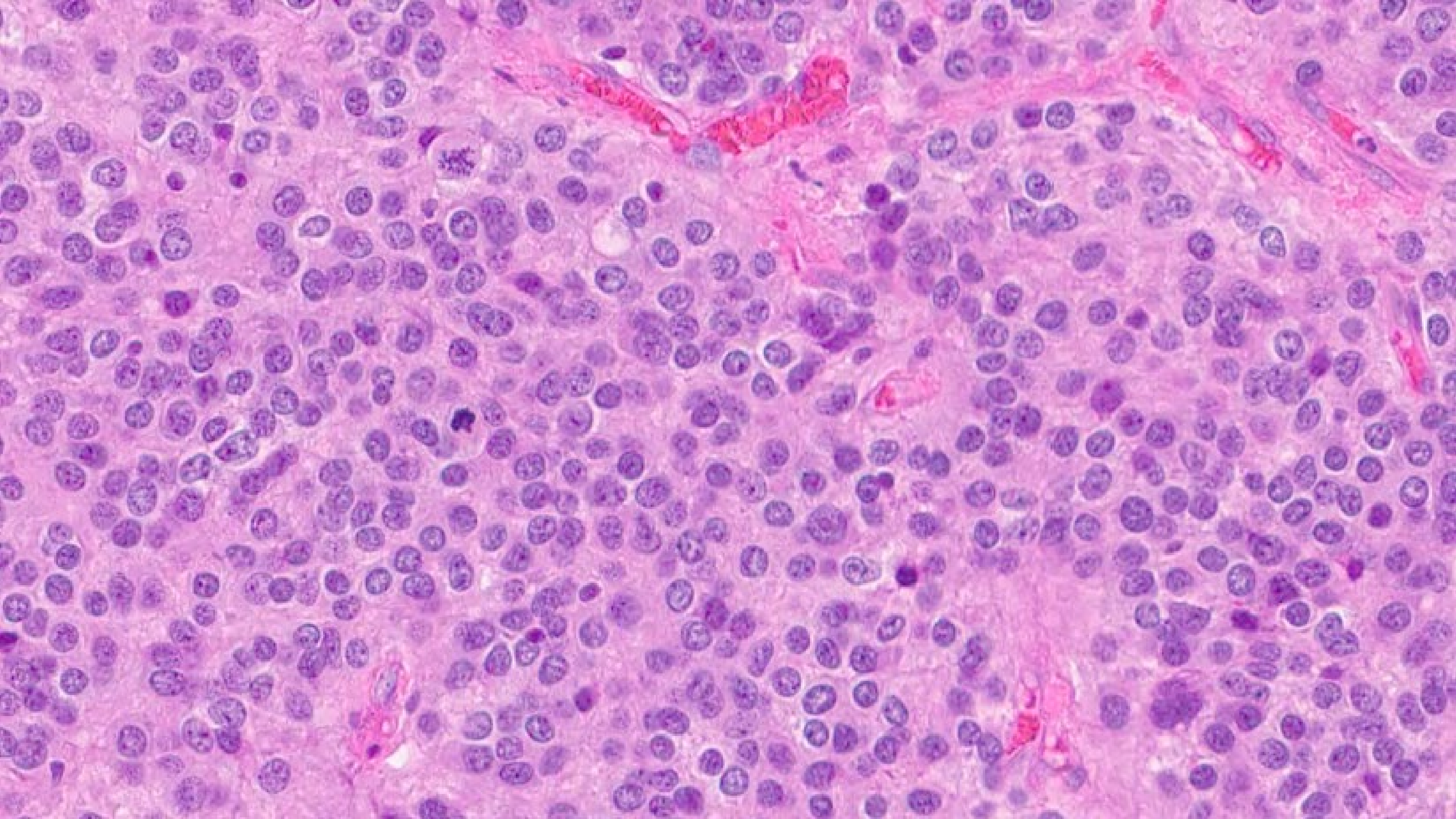




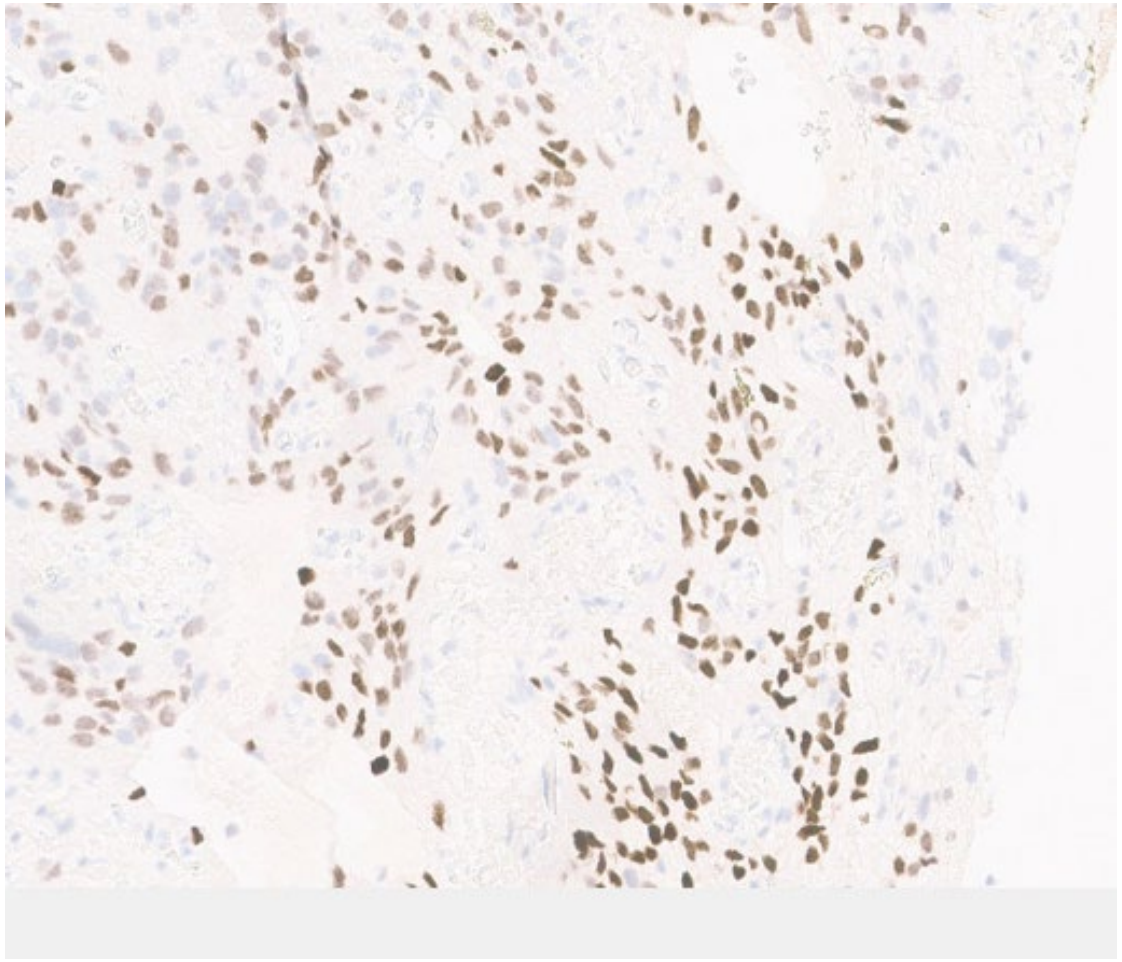




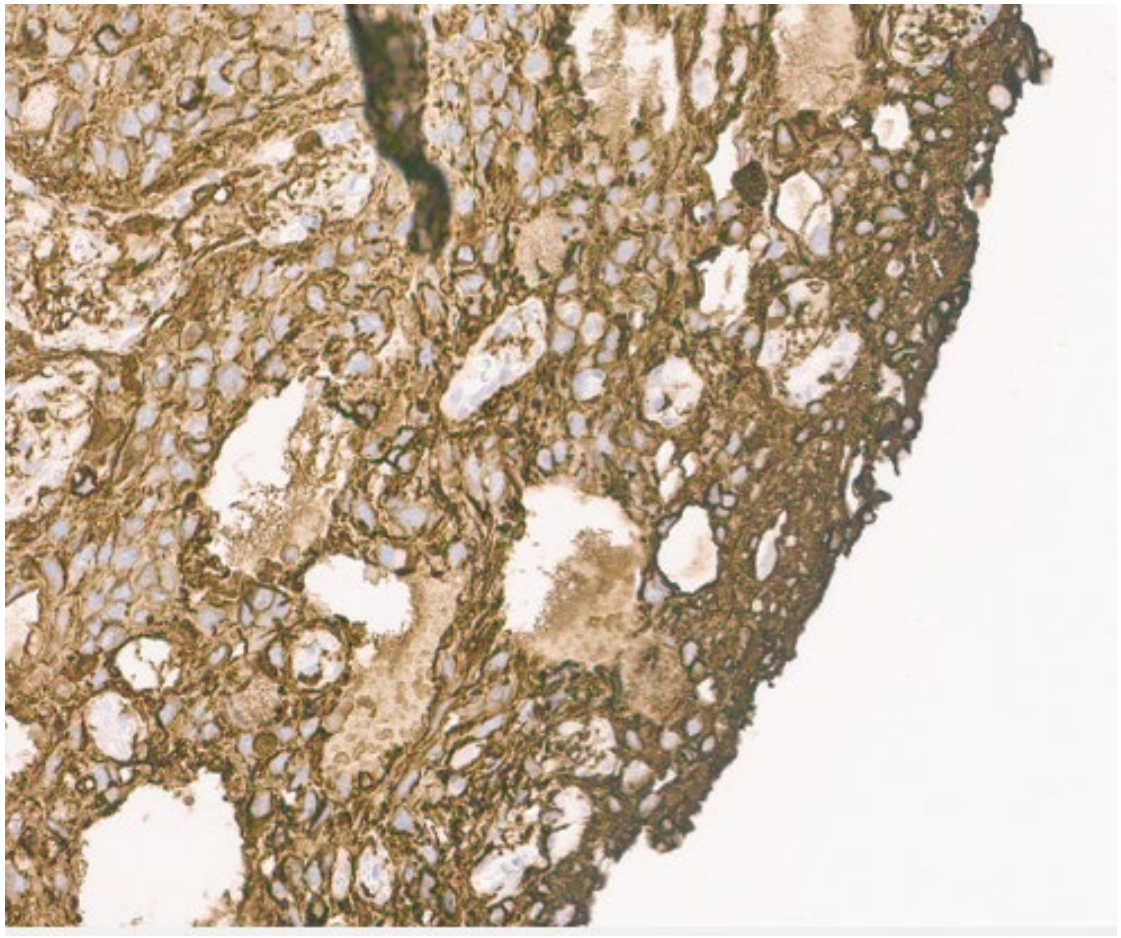




Differential diagnosis?



Olig2



GFAP

Immunohistochemical Workup

Positive

- GFAP
- Olig2

Negative

- P53
- IDH1-R132H
- Synaptophysin
- Chromogranin
- NeuN
- BRAF V600E
- H3 K27M

Retained

- H3 K27me3
- ATRX (subset)

Ancillary Studies

- **TERT promoter mutation (TERT promoter -124C>T)**
- FISH for 1p & 19q shows no co-deletions
- FISH for EGFR shows no amplification
- MGMT promoter methylation is ABSENT

Ancillary Studies

- AKT2 & EWSR1-PATZ1 fusions

NGS TEST: RNA Exome Fusion Panel v1.0

STRUCTURAL VARIANTS: FUSION					
Gene	**Transcripts**	**Genomic Location**	**Reads**	**Pathogenicity Assessment**	**Tier***
EWSR1 - PATZ1 e7 : e1	NM_001163286.2 - NM_032052.2	chr22:29685737 - chr22: 31740542	54	Likely Pathogenic	**Tier 3**
PATZ1 - NIPSNAP1 e1 : e4	NM_032052.2 - NM_003634.4	chr22:31740747 - chr22: 29961074	13	Uncertain Significance	**Tier 3**

*Tier: Actionability Classification

1 - FUSION VARIANT INTERPRETATION

Result: 1 relevant variant is detected in this study.

Summary: EWSR1-PATZ1fusion was detected with a total of 54 reads, and is consistent with a recent study of60 predominantly pediatric CNS neoplasms harboring PATZ1 fusions for which DNA methylation profiling defined a biologically distinct molecular class of histologically polyphenotypic neuroepithelial tumors [PMID: 34417833].

Methylation Profile

- Methylation profile on the version 12.5 of Heidelberg classifier matches to neuroepithelial tumor with PATZ1 fusion with a high confidence score
  - EWSR1-PATZ1 fusion found on NGS is consistent with this methylation class

Integrated Diagnosis

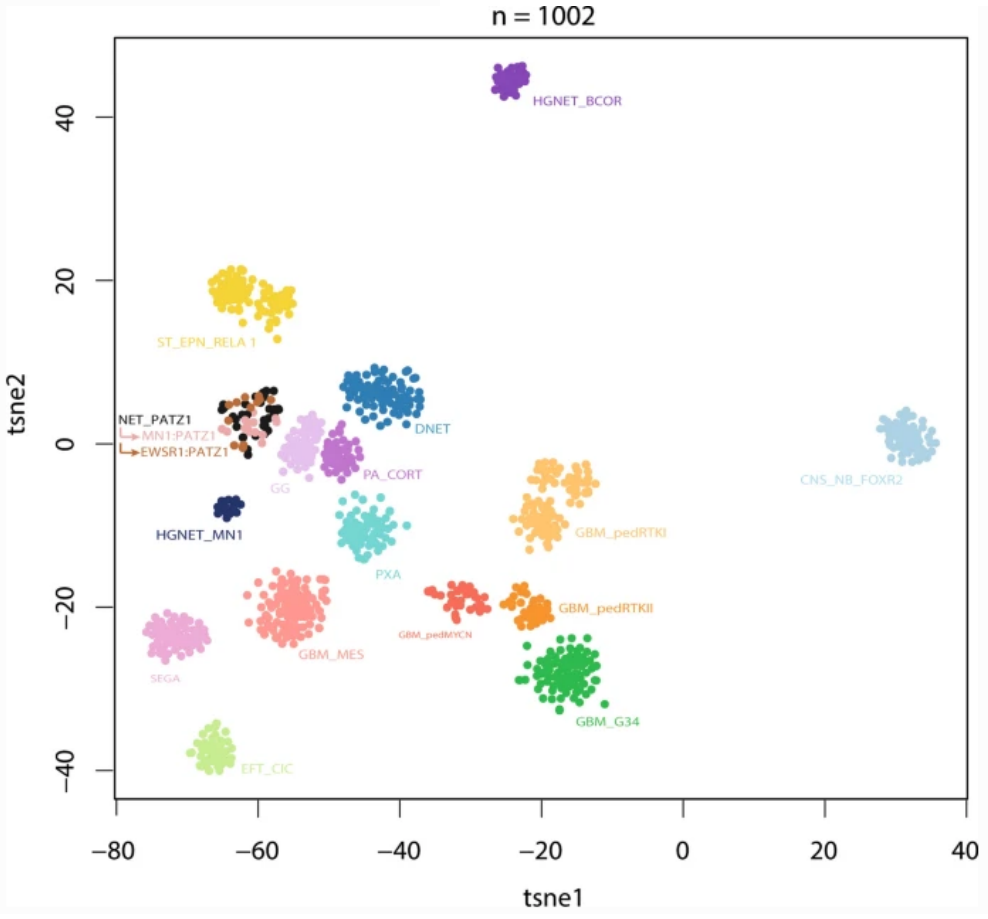
- Neuroepithelial tumor with PATZ1 fusion
  - TERT promoter mutation (TERT promoter -124C>T)
  - MGMT promoter methylation ABSENT
  - AKT2 R371H mutation

Neuroepithelial tumor with PATZ1 fusion

PATZ1 fusions define a novel molecularly distinct neuroepithelial tumor entity with a broad histological spectrum

Karam T. Alhalabi, Damian Stichel, Philipp Sievers, Heike Peterziel, Alexand
Sturm, Andrea Wittmann, Martin Sill, Natalie Jäger, Pengbo Beck, Kristian V
George Jour, Michael Delorenzo, Allison M. Martin, Adam Levy, Nagma Da
G. Gottardo, Emmanuelle Uro-Coste, Claude-Alain Maurage, Catherine Goc
Torsten Pietsch, ... David T. W. Jones + Show authors

- Novel entity
- Histologically heterogenous tumors of different grades
- Varied immunophenotypes



Neuroepithelial tumor with PATZ1 fusion

- Median age at diagnosis 11 years
  - 74% under 18 years
- Located in supratentorial region but rarely in posterior fossa
- Intermediate prognosis
- Currently no therapies available for directly target alterations in EWSR1

Patient Follow-Up

- Completed radiation therapy
- Continues temozolomide

References

- Alhalabi KT, Stichel D, Sievers P, et al. PATZ1 fusions define a novel molecularly distinct neuroepithelial tumor entity with a broad histological spectrum. *Acta Neuropathol*. 2021;142(5):841-857. doi: 10.1007/s00401-021-02354-8.
- Burel-Vandenbos F, Pierron G, Thomas C, et al. A polyphenotypic malignant paediatric brain tumour presenting a MN1-PATZ1 fusion, no epigenetic similarities with CNS High-Grade Neuroepithelial Tumour with MN1 Alteration (CNS HGNET-MN1) and related to PATZ1-fused sarcomas. *Neuropathol Appl Neurobiol*. 2020;46(5):506-509. doi: 10.1111/nan.12626.
- Siegfried A, Rousseau A, Maurage CA, et al. EWSR1-PATZ1 gene fusion may define a new glioneuronal tumor entity. *Brain Pathol*. 2019;29(1):53-62. doi: 10.1111/bpa.12619.
- Tauziède-Espariat A, Chotard G, le Loarer F, et al. A novel LARGE1-AFF2 fusion expanding the molecular alterations associated with the methylation class of neuroepithelial tumors with PATZ1 fusions. *Acta Neuropathol Commun*. 2022;10(1):15. doi: 10.1186/s40478-022-01317-8.