2022-9

Angus Toland, M.D.
Neuropathology Fellow
Stanford Health Care

Donald Born, M.D., Ph.D.
Clinical Professor, Neuropathology
Stanford Health Care

Stanford MEDICINE

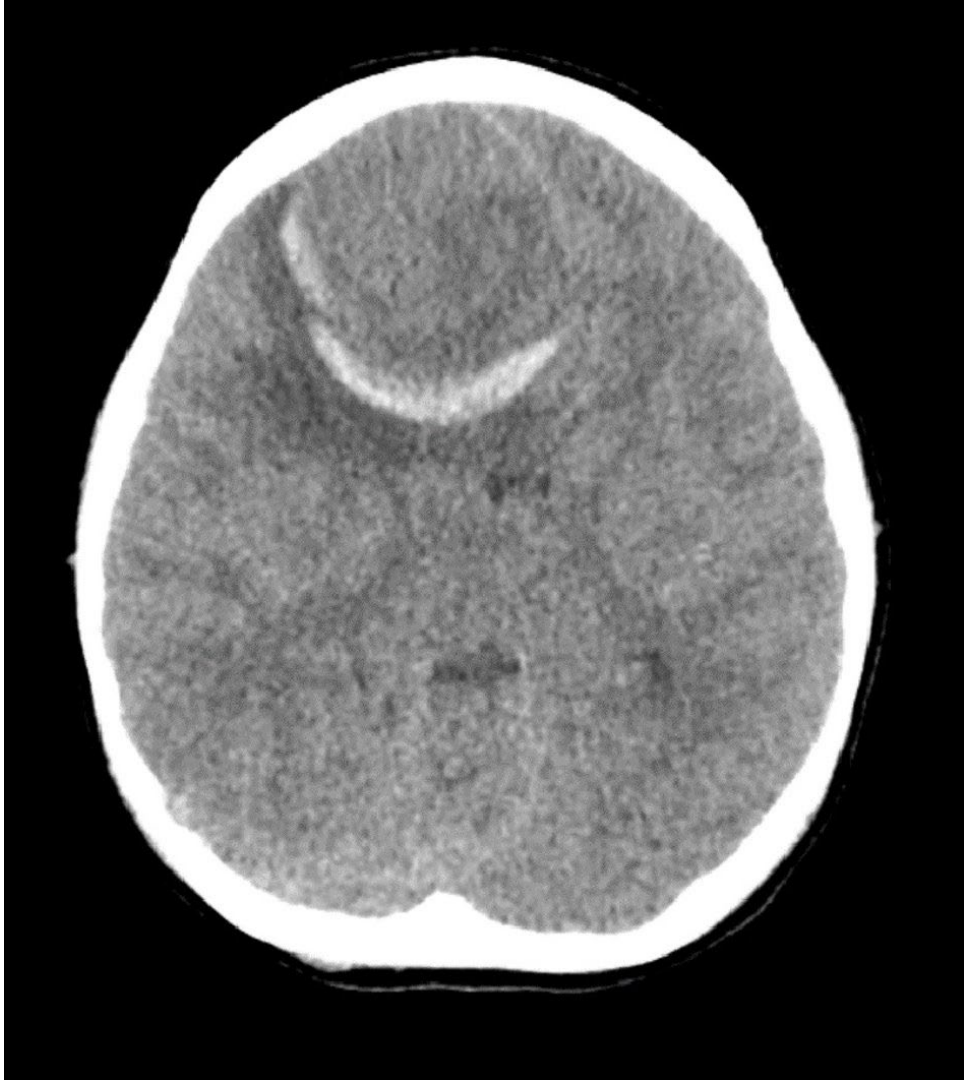
Clinical Summary

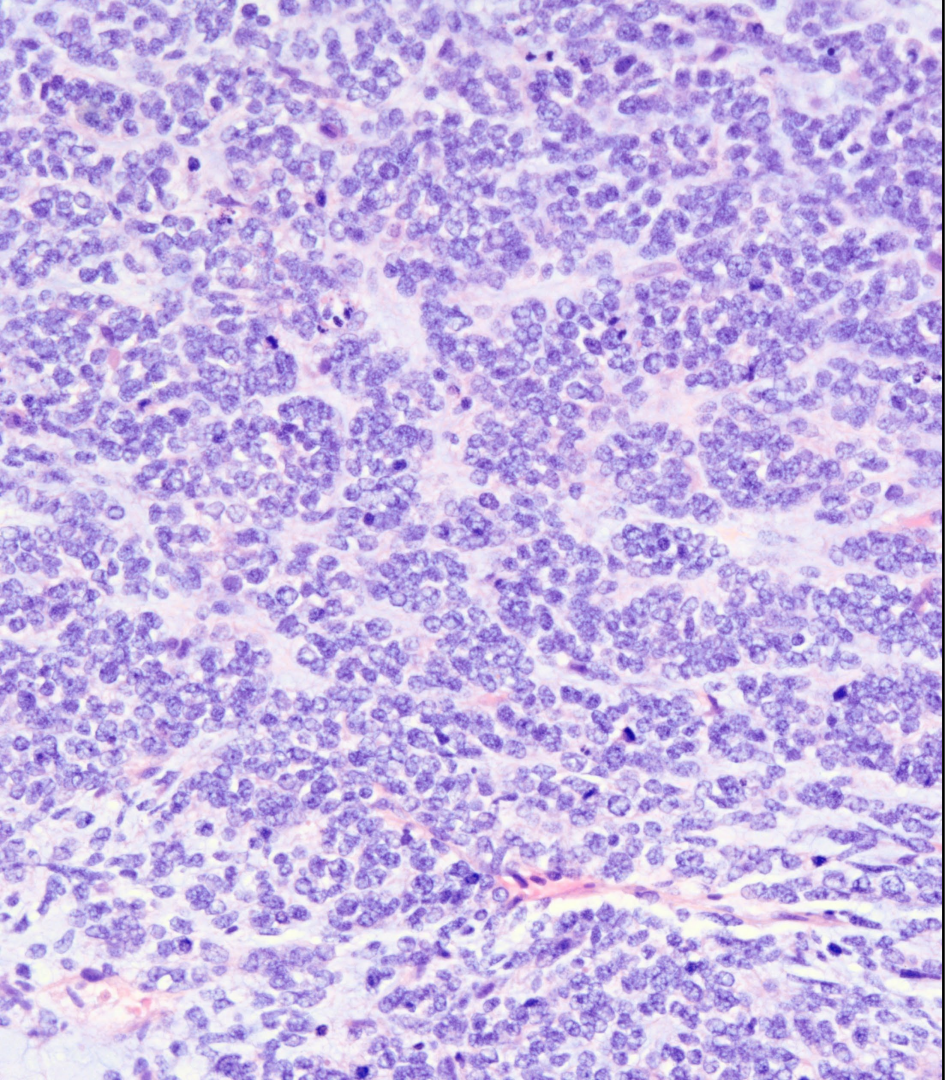
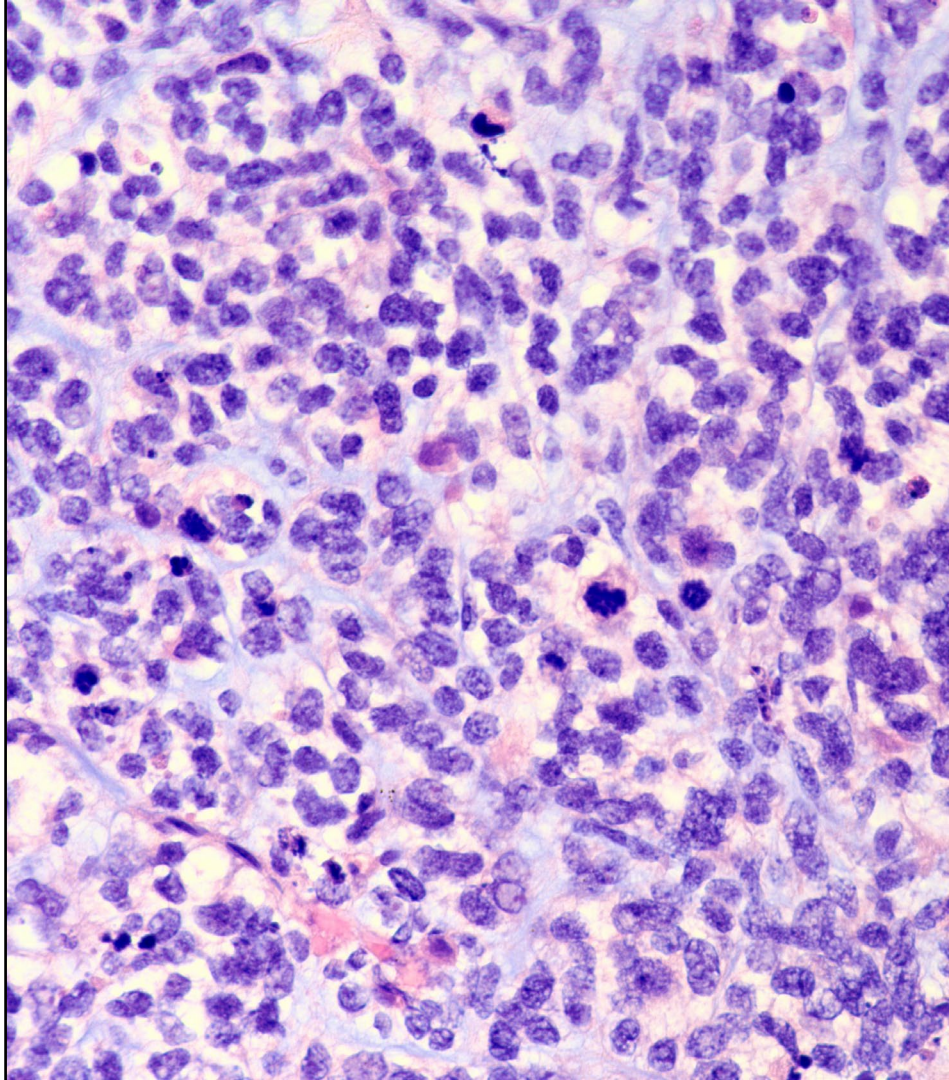
- 5-year-old boy who presented with acute-onset nausea and vomiting
- Initially believed to have appendicitis, but later developed a fixed, dilated right pupil

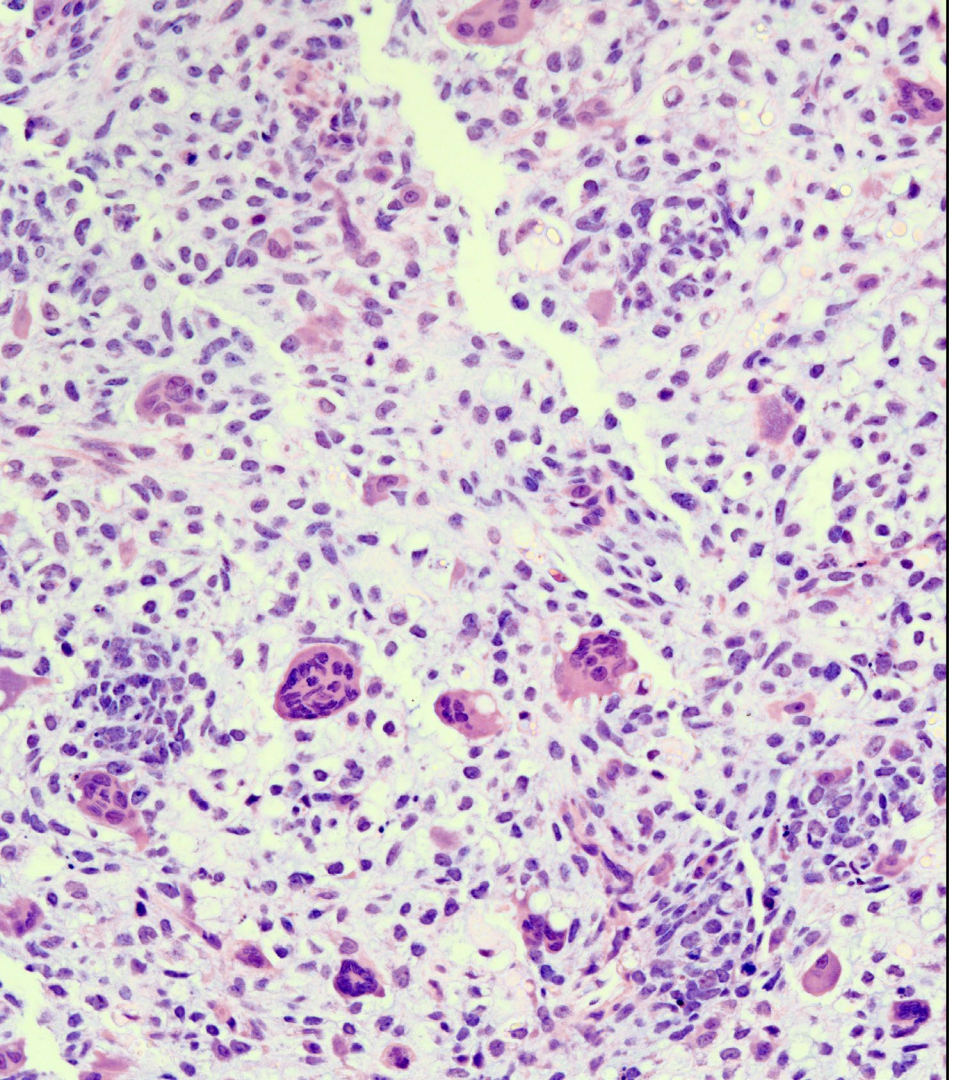
Stanford MEDICINE

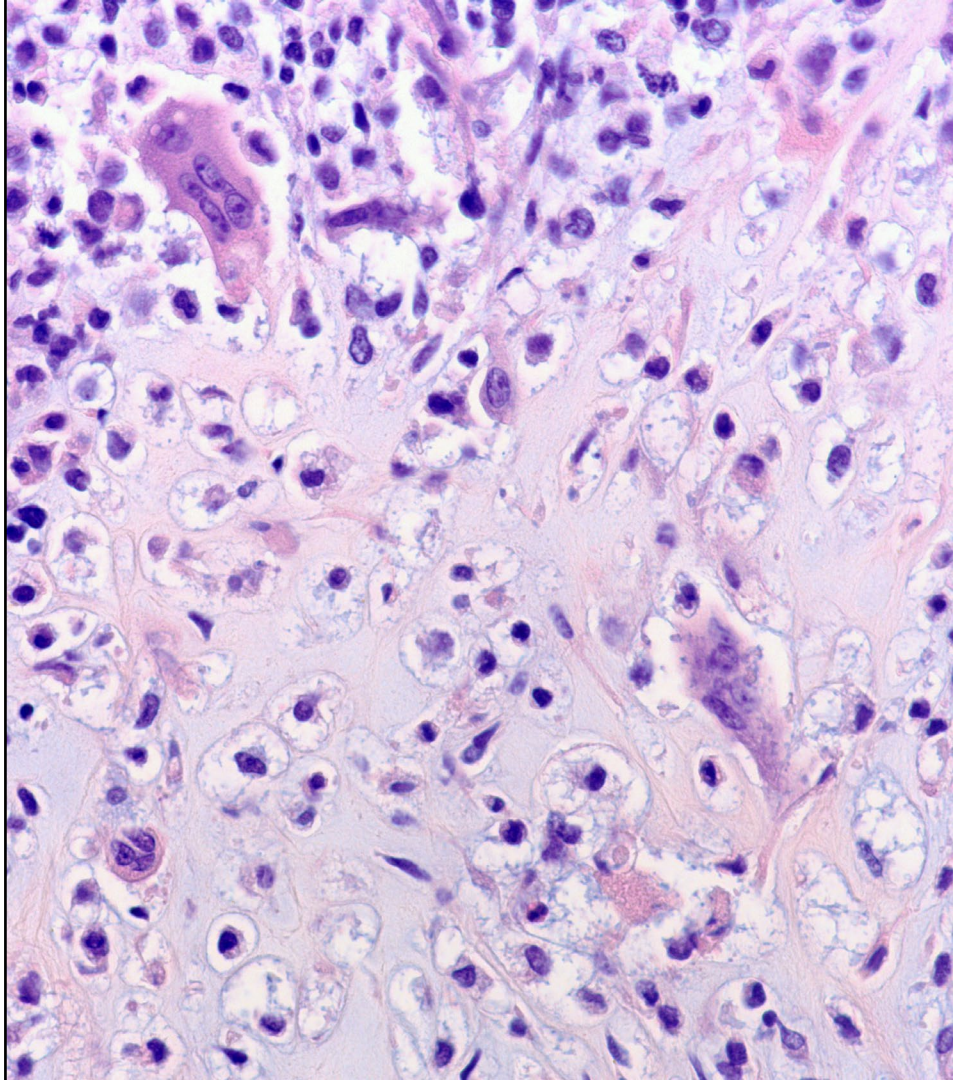
Imaging

- CT demonstrated right frontal mass with sulcal effacement, midline shift, and early herniation
- DDx: Abscess vs tumor
- Mass was resected
  - Described as gelatinous and friable, non-infiltrating intraparenchymal mass
  - No bony or dural attachment



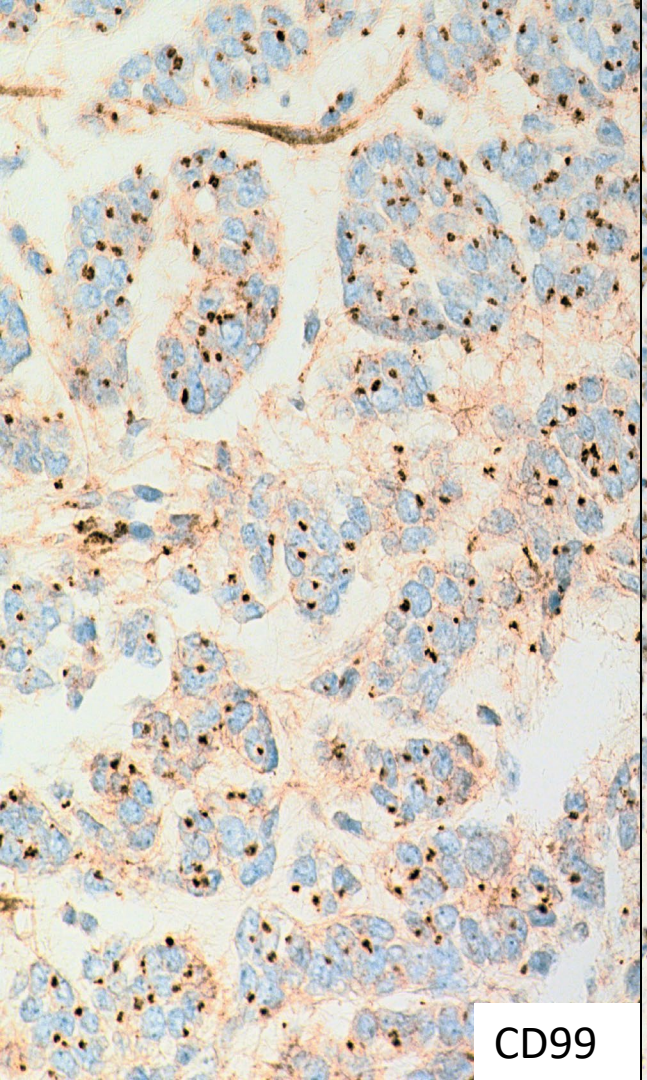


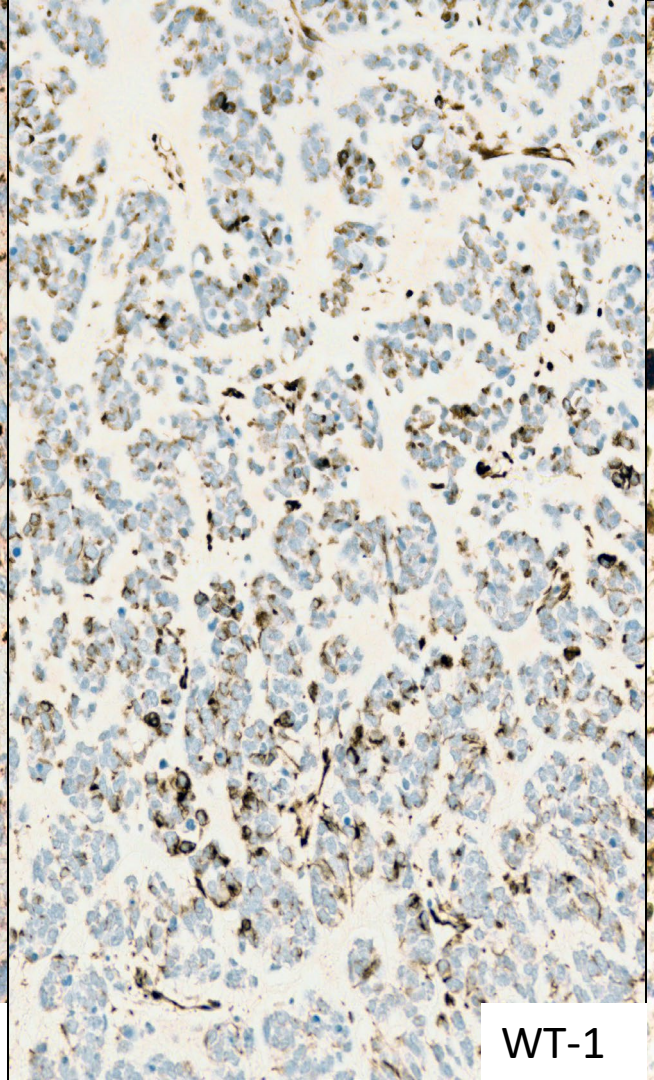


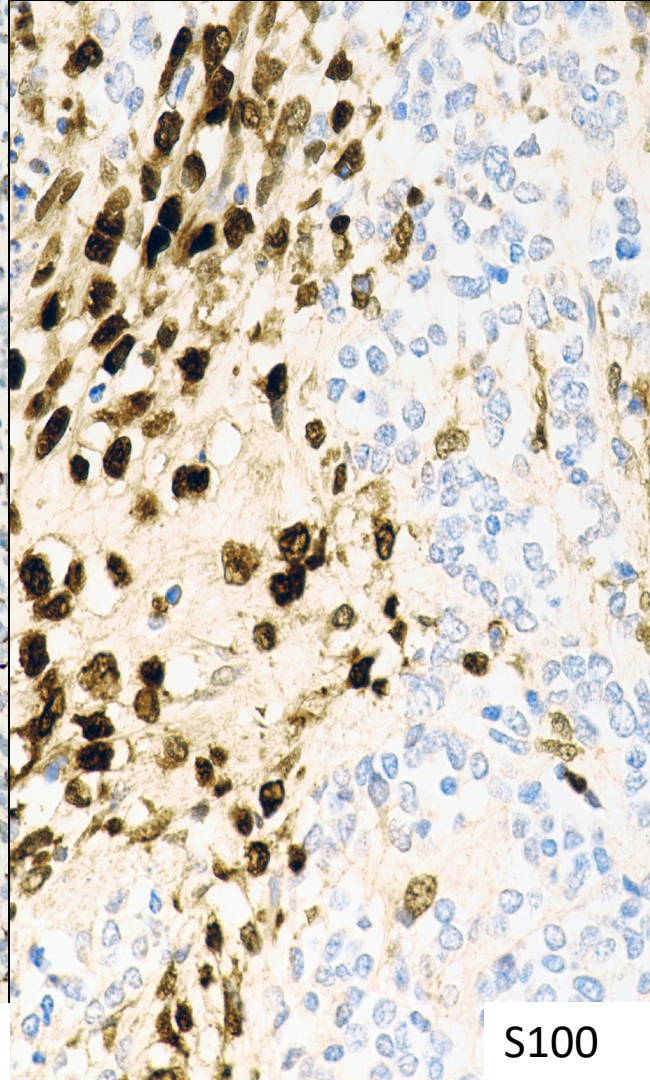
Differential Diagnosis?

- Immunohistochemical stains?

Stanford MEDICINE


CD99

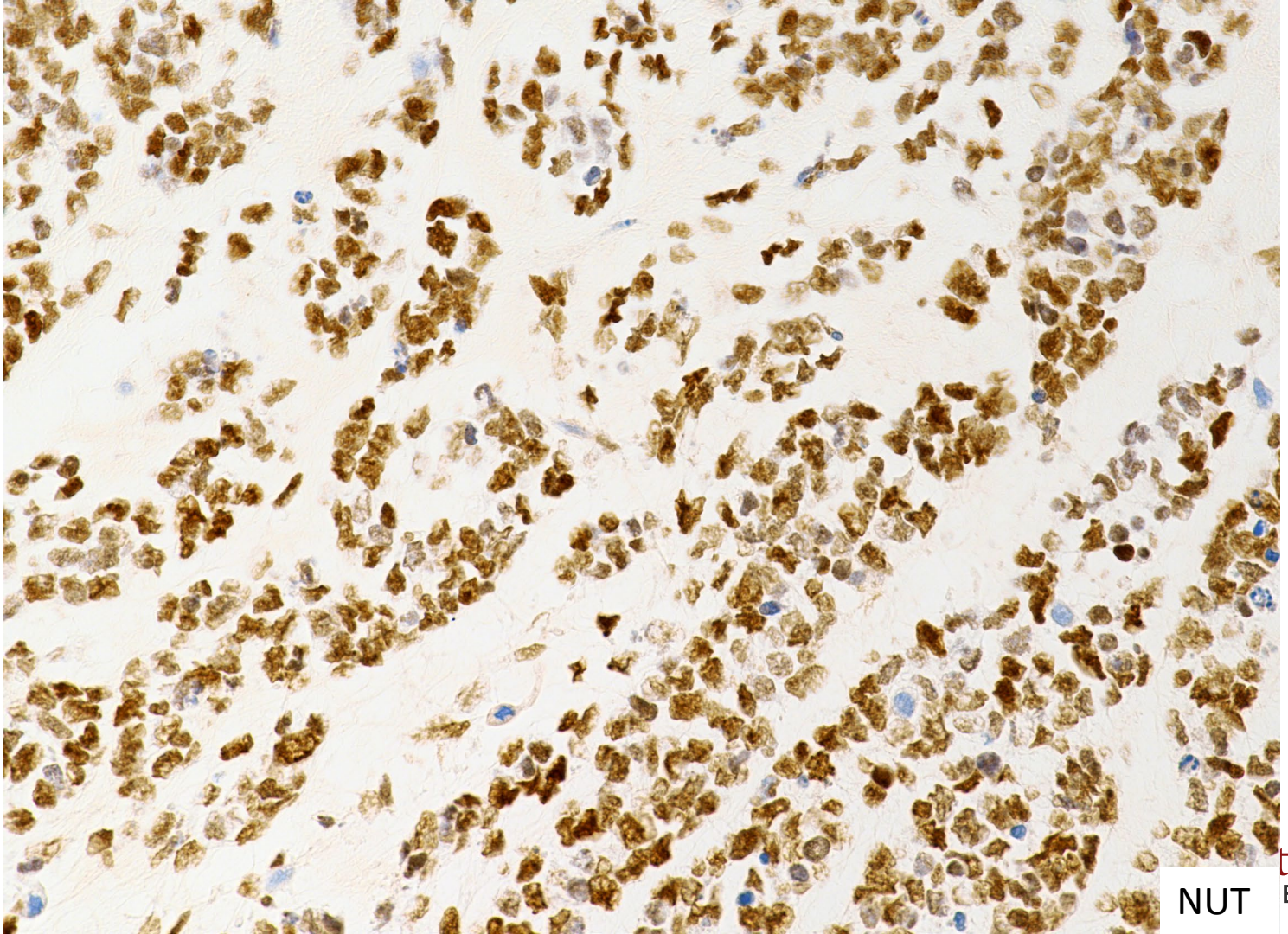

WT-1


S100

Immunohistochemical work-up

Positive	Negative
INI1/BRG (Retained)	GFAP
CD99 (weak, dot-like)	EMA
S100 (restricted to chondroid areas)	NKX3.1
WT-1 (patchy, cytoplasmic)	Synaptophysin
	SALL4
	Mixed CK (AE1/CAM5.2)

Stanford MEDICINE



NUT

tanford
EDICINE

Molecular testing

- CIC-NUTM1 fusion with rearrangement of exon 17
  - No additional pathogenic/likely pathogenic alterations
- Methylation profiling matched to CIC-rearranged sarcoma

Stanford MEDICINE

CIC-rearranged Sarcoma

- Recent addition to the WHO; previously described with “Ewing-like sarcomas”
- Rare sarcoma arising in the central nervous system
  - May be bone, dural, or parenchymal-based
  - Identical tumor in peripheral soft tissues and viscera (rarely bone), frequently harboring *CIC-DUX4* fusion
- Typically a tumor of adolescents and young adults, though reported age range is wide

Stanford MEDICINE

- Typically described as a poorly-differentiated sarcoma
  - Epithelioid to spindled cells with hyperchromatic, irregular nuclei and variable eosinophilic cytoplasm generally arranged as sheets or cords
  - Myxoid background is frequently reported
  - Numerous mitotic figures and karyorrhectic cells present
  - Well-demarcated border with surrounding brain/spinal cord parenchyma
- Immunohistochemistry shows no clear line of differentiation
  - CD99+ (membranous or dot-like), WT-1 +/-
  - ETV4 positivity is reported in most cases
    - ETV3 and ETV5 expression is also present
  - Negative for S100, SOX10, PAX7, GFAP, NKX2.2, Synaptophysin
- Variety of fusions reported; histology, immunophenotype, and methylation overlap
  - *CIC-NUTM1*
  - *CIC-NUTM2*
  - *CIC-DUX4*
  - *ATXN1-NUTM1*
  - *ATXN1-DUX4*

MODERN PATHOLOGY (2016) 29, 1523–1531

ETV4 is a useful marker for the diagnosis of *CIC*-rearranged undifferentiated round-cell sarcomas: a study of 127 cases including mimicking lesions

Sophie Le Guellec[1,2], Valérie Velasco[3], Gaëlle Pérot[2,3], Sarah Watson[4], Franck Tirode[4] and Jean-Michel Coindre[2,3,5]

[1]*Department of Pathology, Institut Claudius Regaud, Institut Universitaire du Cancer Toulouse-Oncopole, Toulouse, France;* [2]*INSERM U916, Institut Bergonié, Bordeaux, France;* [3]*Department of Biopathology, Institut Bergonié, Bordeaux, France;* [4]*INSERM U830, Laboratory of Genetics and Biology of Cancer, Institut Curie, Paris, France and* [5]*Université de Bordeaux, Bordeaux, France*

Table 2 Immunohistochemical features of CIC-rearranged round-cell sarcomas

Case	*CD99*	*Cyclin B3 (%, intensity, location)*	*Fli1 (%, intensity, location)*	*ERG (%, intensity, location)*	*WT1 (N-TER) (%, intensity, location)*	*WT1 (C-TER) (%, intensity, location)*	*ETV4 (%, intensity, location)*
1	Negative	Negative	ND	ND	Negative	ND	100, 3+, N
2	Focal	Negative	Negative	ND	100, 3+, C	100, 3+, N	100, 3+, N
3	Negative	Negative	ND	ND	Negative	Negative	100, 3+, N
4	Pos, m	Negative	ND	ND	100, 3+, C	100, 3+, N	100, 3+, N
5	Pos, m	Negative	ND	ND	100, 3+, C	Negative	80, 3+, N
6	Negative	Negative	Negative	Negative	100, 3+, C	100, 3+, N	100, 3+, N
7	Negative	Negative	5, 1+, N	Negative	100, 3+, C+N	100, 3+, N	100, 3+, N
8	Negative	Negative	Negative	Negative	100, 3+, C	Negative	100, 3+, N
9	Negative	Negative	ND	Negative	Negative	ND	100, 3+, N
10	ND	Negative	5, 1+, N	Negative	100, 3+, C	ND	100, 3+, N
11	Pos, m	Negative	ND	ND	100, 3+, C	100, 3+, N	100, 3+, N
12	Focal	Negative	ND	ND	100, 3+, C	ND	100, 3+, N
13	ND	Negative	ND	Negative	100, 3+, C	100, 3+, N	100, 3+, N
14	Pos, m	Negative	Negative	10, 1+, N	100, 3+, C	100, 3+, N	100, 3+, N
15	Negative	Negative	ND	ND	100, 3+, C	ND	100, 3+, N
16	Focal	Negative	Negative	Negative	100, 3+, C	100, 3+, N	80, 3+, N
17	Negative	Negative	Negative	Negative	100, 3+, C	100, 3+, N	100, 3+, N

Abbreviations: C, cytoplasmic; Pos, m, membranous positivity; N, nuclear; ND, not done.

Chondroid Differentiation

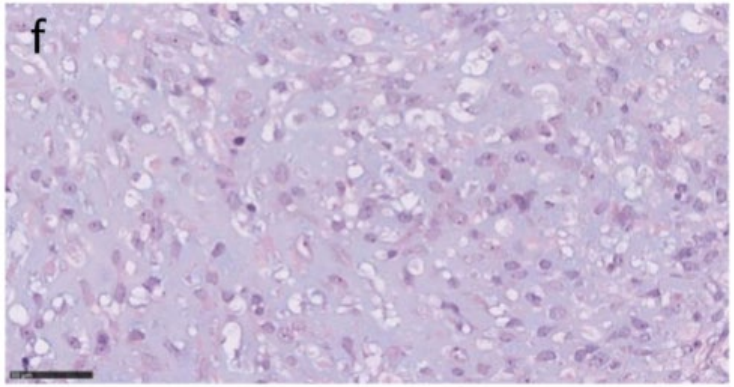
Siegfried *et al. Acta Neuropathologica Communications* (2019) 7:220
https://doi.org/10.1186/s40478-019-0870-8

Acta Neuropathologica Communications

LETTER TO THE EDITOR Open Access

Brain tumor with an *ATXN1-NUTM1* fusion gene expands the histologic spectrum of *NUTM1*-rearranged neoplasia

Aurore Siegfried[1,2], Julien Masliah-Planchon[3,4], Franck-Emmanuel Roux[1], Delphine Larrieu-Ciron[1], Gaelle Pierron[5], Yvan Nicaise[2], Marion Gambart[1], Isabelle Catalaa[1], Sarah Péricart[1], Charlotte Dubucs[1], Badreddine Mohand-Oumoussa[6], Franck Tirode[7], Franck Bourdeaut[3,4] and Emmanuelle Uro-Coste[1,2*]



*Adapted from Siegfried et. al. figure 1

Published in final edited form as:
Genes Chromosomes Cancer. 2018 September ; 57(9): 446–451. doi:10.1002/gcc.3.

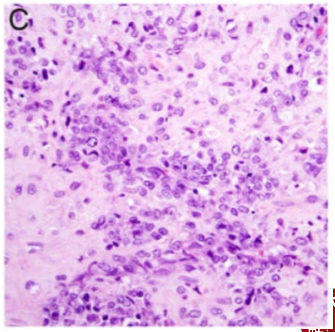
CIC-NUTM1 fusion: A case which expands the spectrum of *NUT*-rearranged epithelioid malignancies

Inga-Marie Schaefer[1], Paola Dal Cin[1], Latrice M. Landry[2], Christopher D. M. Fletcher[1], Glenn J. Hanna[3], Christopher A. French[1]

[1]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

[2]Center for Advanced Molecular Diagnostics, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

[3]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts



*Adapted from Schaefer et. al. figure 2

Stanford MEDICINE

Differential diagnosis

- Ewing sarcoma-CD99 diffuse membranous expression, ETV4 negative, *EWSR1* rearrangement
- Atypical teratoid/rhabdoid tumor-INI1/BRG1 loss
- Mesenchymal chondrosarcoma-*HEY1-NCOA2* fusion
- Extraskeletal myxoid chondrosarcoma-INSM1+, *EWSR1-NR4A3* rearrangement typical
- High-grade glioma-GFAP, OLIG2+; primitive neuronal component-*RB1* loss/*MYCN* or *MYC* amplification

Stanford MEDICINE

References

- Yamada S, Muto J, et. al. Primary spinal intramedullary Ewing-like sarcoma harboring CIC-DUX4 translocation: a similar cytological appearance as its soft tissue counterpart but no lobulation in association with desmoplastic stroma. Brain Tumor Pathol. 2020 Jul;37(3):111-117.
- Sugita S, Arai Y, et. al. NUTM2A-CIC fusion small round cell sarcoma: a genetically distinct variant of CIC-rearranged sarcoma. Hum Pathol. 2017 Jul;65:225-230.
- Luo W, Stevens TM, et. al. *NUTM1*-Rearranged Neoplasms-A Heterogeneous Group of Primitive Tumors with Expanding Spectrum of Histology and Molecular Alterations-An Updated Review. Curr Oncol. 2021 Nov 7;28(6):4485-4503.
- Le Guellec S, Velasco V, et. al. ETV4 is a useful marker for the diagnosis of CIC-rearranged undifferentiated round-cell sarcomas: a study of 127 cases including mimicking lesions. Mod Pathol. 2016 Dec;29(12):1523-1531.
- Le Loarer F, Pissaloux D, et. al. Clinicopathologic Features of CIC-NUTM1 Sarcomas, a New Molecular Variant of the Family of CIC-Fused Sarcomas. Am J Surg Pathol. 2019 Feb;43(2):268-276.
- Mangray S, Kelly DR, et. al. Clinicopathologic Features of a Series of Primary Renal CIC-rearranged Sarcomas With Comprehensive Molecular Analysis. Am J Surg Pathol. 2018 Oct;42(10):1360-1369.
- Schaefer IM, Dal Cin P, et. al. CIC-NUTM1 fusion: A case which expands the spectrum of NUT-rearranged epithelioid malignancies. Genes Chromosomes Cancer. 2018 Sep;57(9):446-451.
- Siegfried A, Masliah-Planchon J, et. al. Brain tumor with an ATXN1-NUTM1 fusion gene expands the histologic spectrum of NUTM1-rearranged neoplasia. Acta Neuropathol Commun. 2019 Dec 30;7(1):220.
- Pratt D, Kumar-Sinha C, et. al. A novel ATXN1-DUX4 fusion expands the spectrum of 'CIC-rearranged sarcoma' of the CNS to include non-CIC alterations. Acta Neuropathol. 2021 Apr;141(4):619-622.

Stanford MEDICINE