Penn Medicine

MMIHICC 2025

Clinical Information

5-month-old male with history of two episodes of focal seizures, fever, and associated upper respiratory symptoms.

Physical exam revealed left arm weakness (right hand preference) and mild left facial droop.

Past History:

Antenatal & Postnatal History: Full term and developing normally

Immunization History: up to date and received RSV vaccine

Nutritional History: poor intake on day of presentation, otherwise normal

Family History: No history of malignancy or known genetic disorder

Laboratory work up:

- CBC and BMP normal
- Infectious workup negative

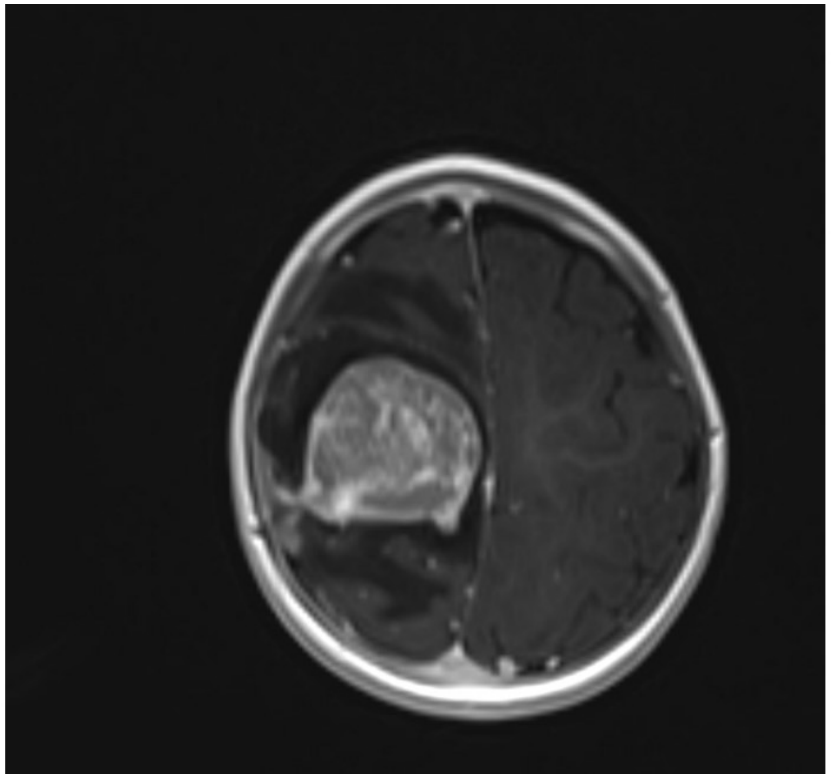
Penn Medicine

Ragiology Images

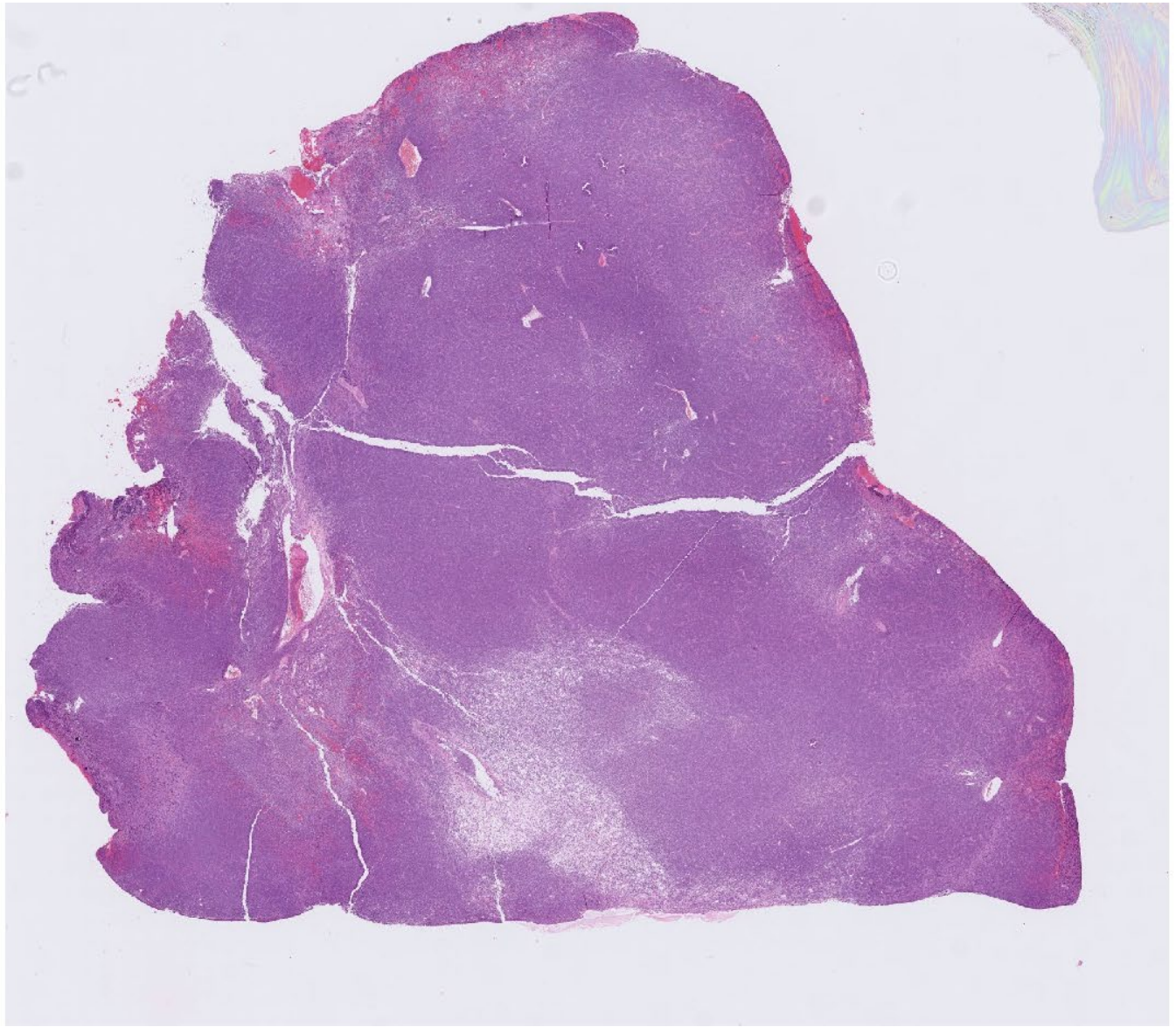
- CT scan and MRI brain identified a large right frontoparietal mass (3.7 x 3.7 x 2.9 cm) involving the corpus callosum and mass effect to right thalamus as well as right ventricle.

Differential Diagnosis:

- Ganglioneuronal tumor (desmoplastic infantile ganglioglioma)
- Sarcoma

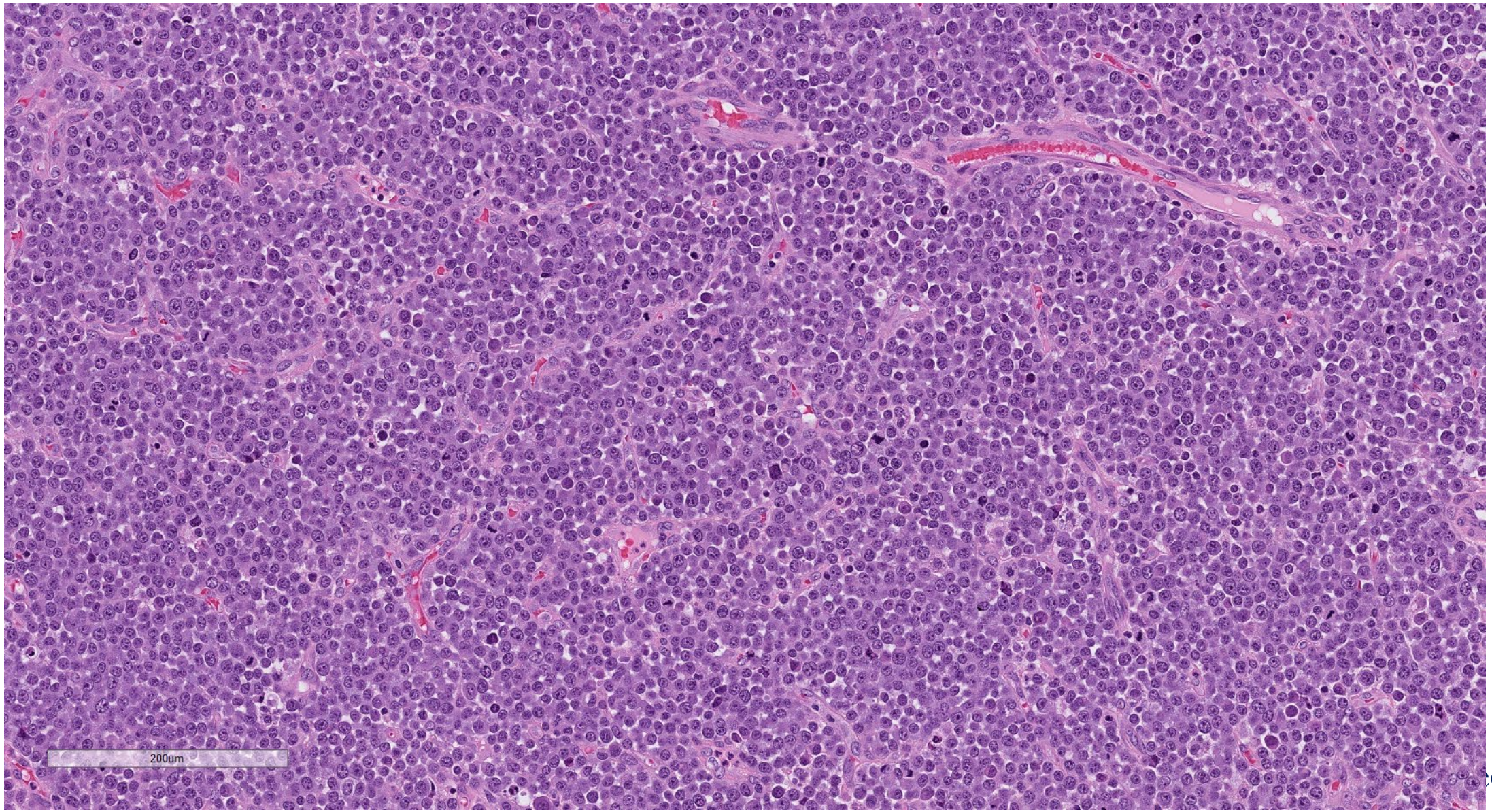


Histopathology



Medicine

Histopathology

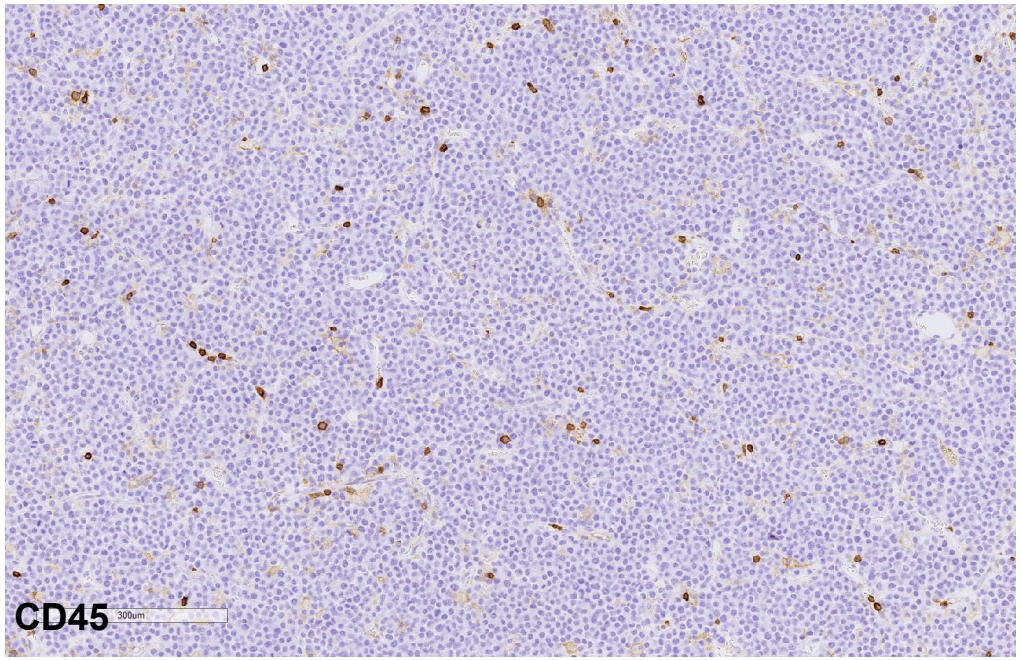


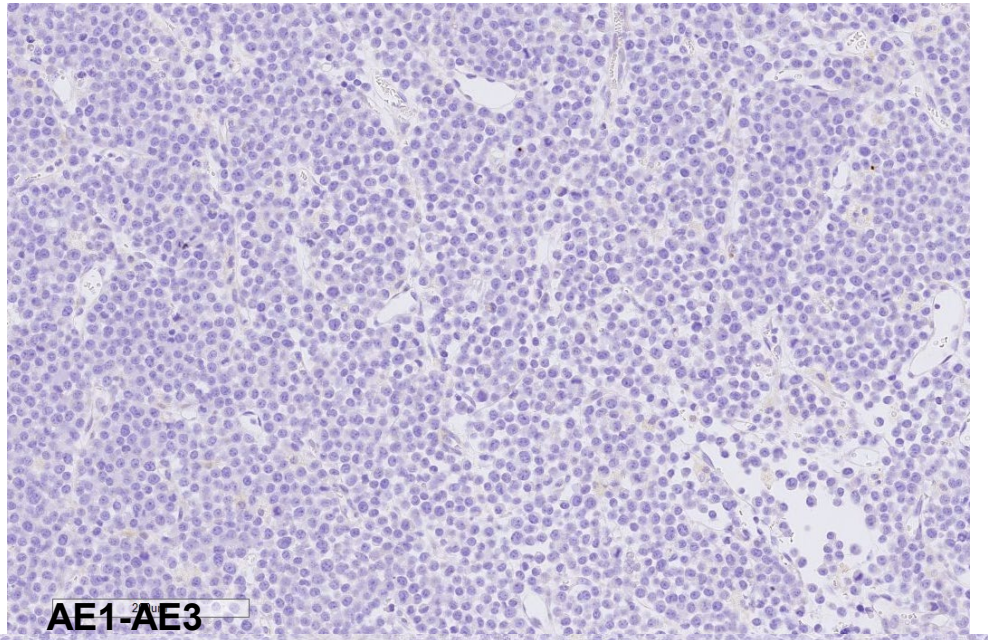
Differential Diagnosis [CNS Small Round Blue Cell Morphology]

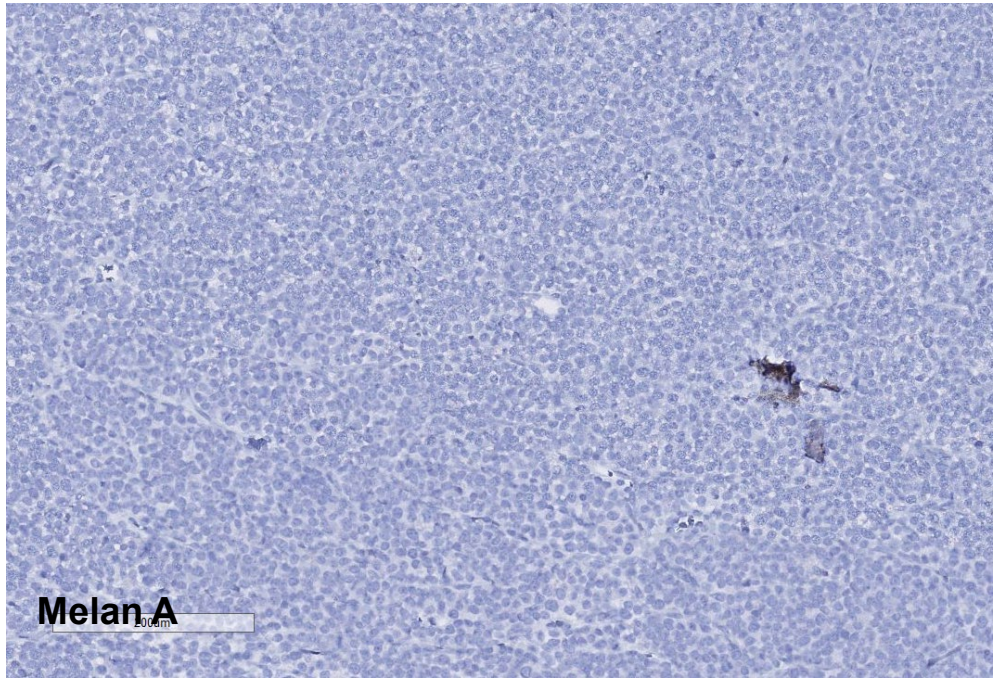
Tumor Type	Age, Site, Morphology	IHC
Desmoplastic infantile ganglioglioma (DIG)	<2y & frontoparietal Desmoplastic component mixture of fibroblast-like cells and neuroepithelial cells	GFAP, synaptophysin, NSE negative
Embryonal tumor (Medulloblastoma, PNET)	Cerebellum & fourth ventricle, small round blue cell morphology	NE markers, NSE negative
Lymphoma (LGBCL/ALCL)	Rare primary CNS lymphoma, Discohesive blue cell morphology with centroblasts, immunoblasts, anaplastic cells	CD45, CD3 (other pan T markers), CD30, ALK1, PAX5, others negative
Rhabdomyosarcoma	Rare as primary CNS, undifferentiated small round blue cells	Desmin, Myogenin neg
Ewing's Sarcoma family tumor CIC-rearranged Sarcoma	Wide age range (common in children), soft tissue extremities, Undifferentiated round cell sarcoma,	NKX2.2, CD99, ERG, WT1 negative
Melanoma		HMB45, Melan A, S100 negative
Lymphoblastic leukemia/less likely myeloid sarcoma	High N/C ratio, fine chromatin, prominent nucleoli	CD34, Tdt, CD19, PAX5, CD3, MPO, lysozyme negative
Poorly Differentiated Carcinoma	Primary vs mets with blue cell morphology	AE1-3 and PanCK negative
CNS germ cell tumor	Germinoma common in pineal and suprasellar regions, poorly differentiated tumor cells	OCT3/4, SAL4 negative

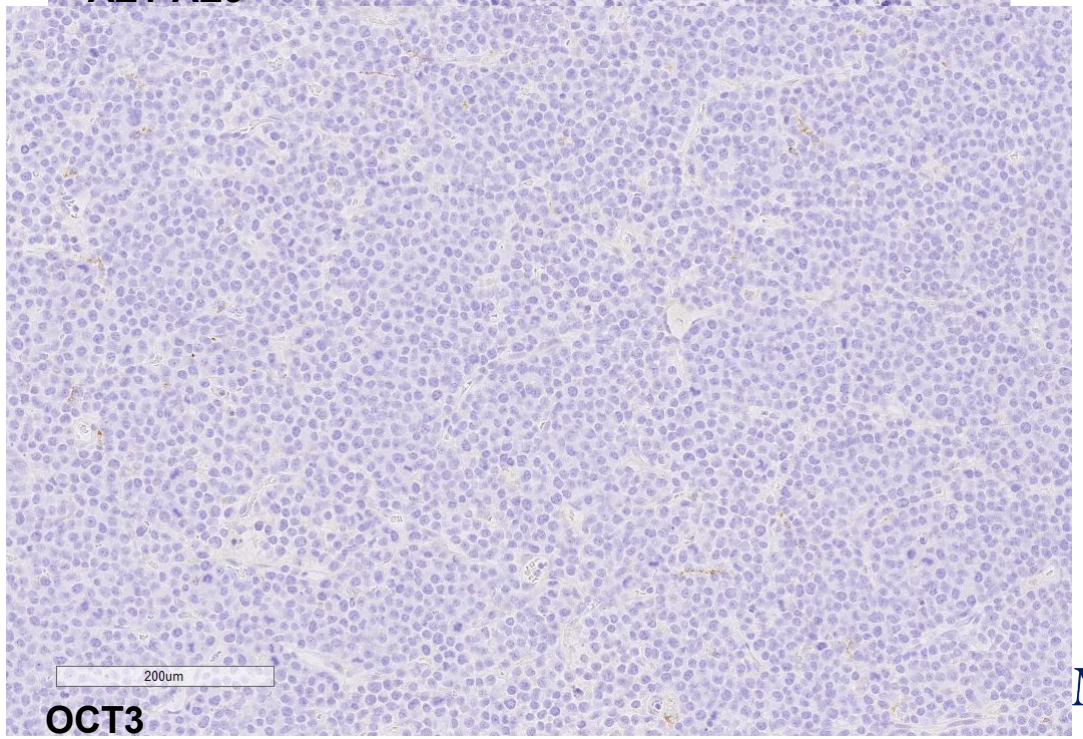
Other markers with retained expression: INI-1, BRG-1, ATRX H3K27me3

Penn Medicine

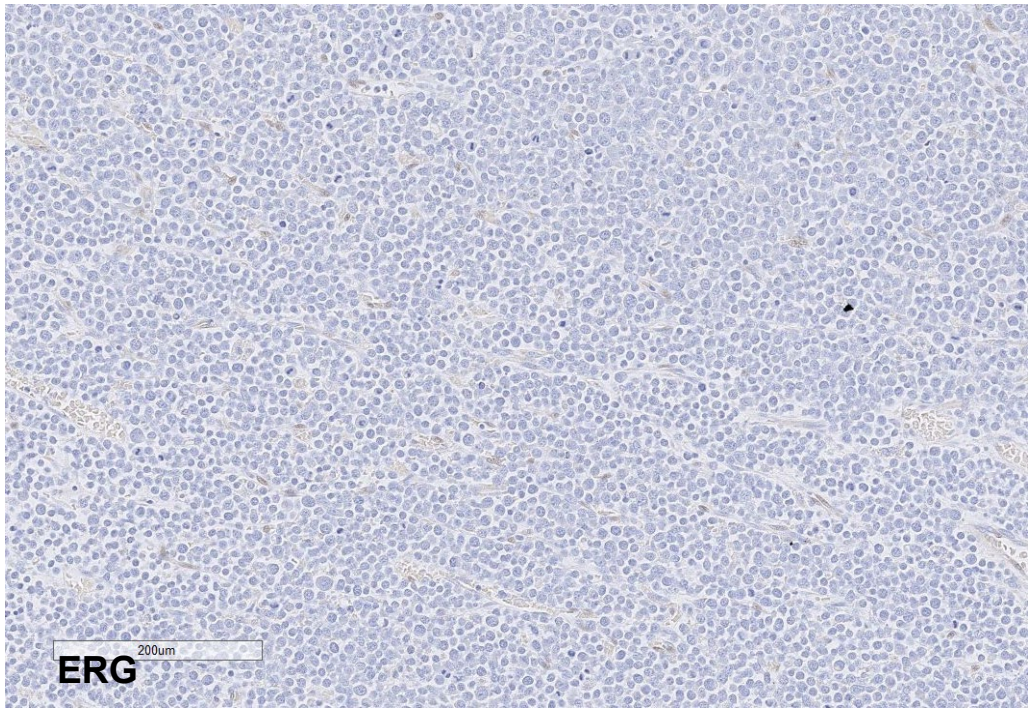


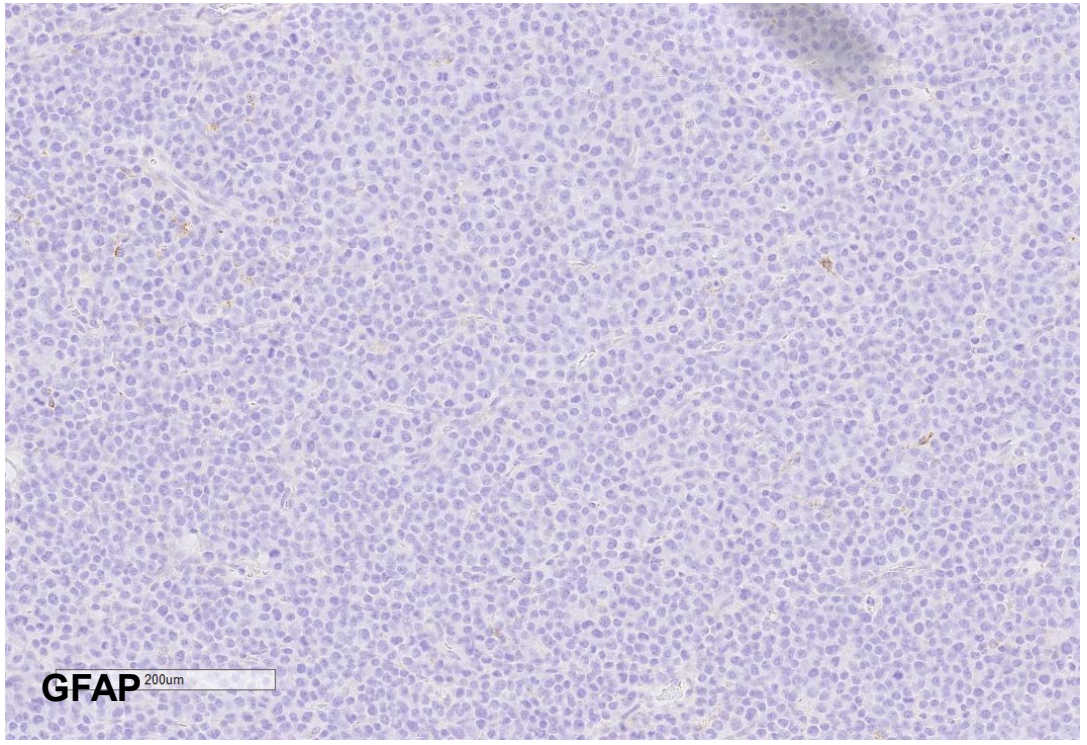


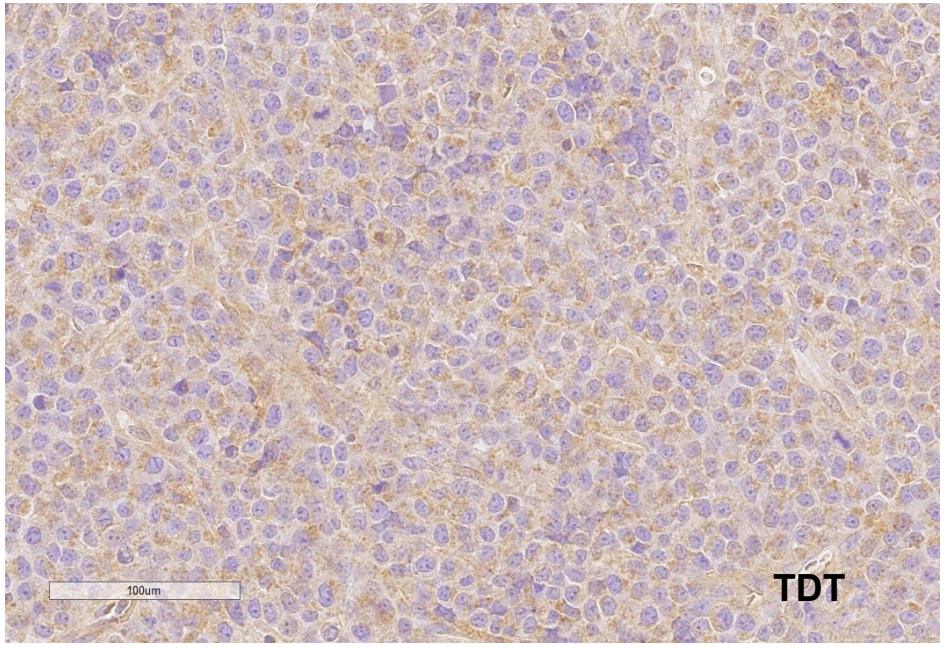


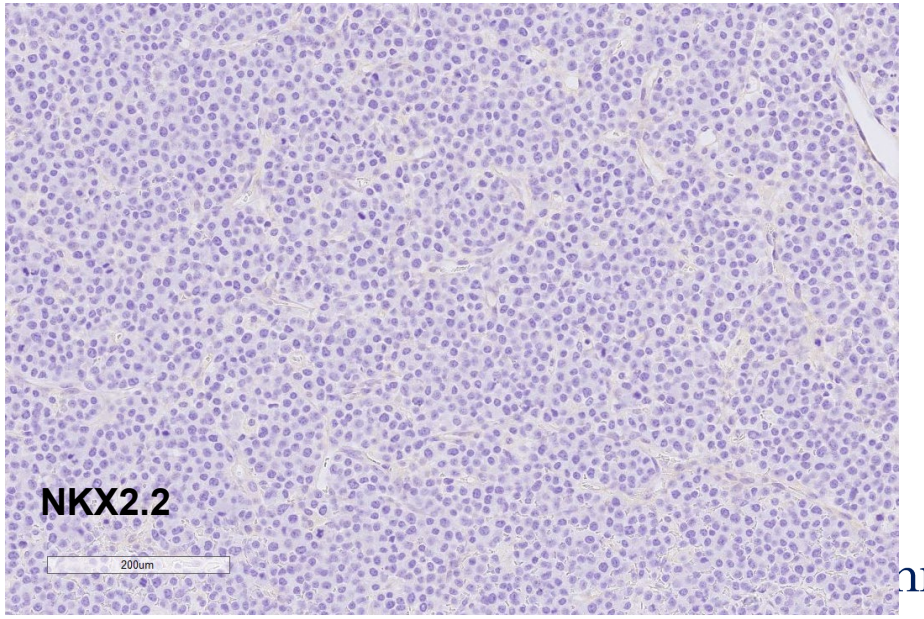


Medicine

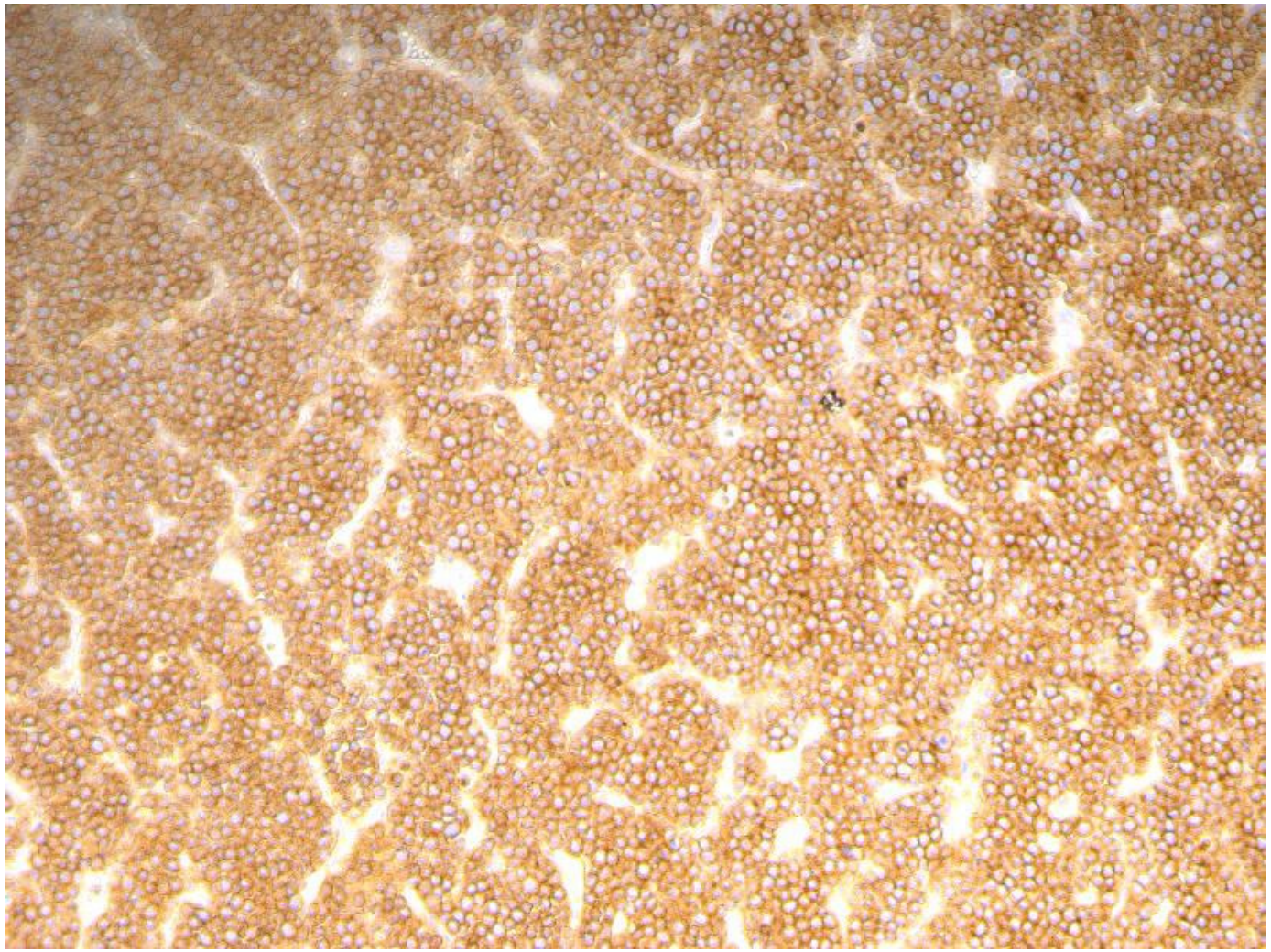






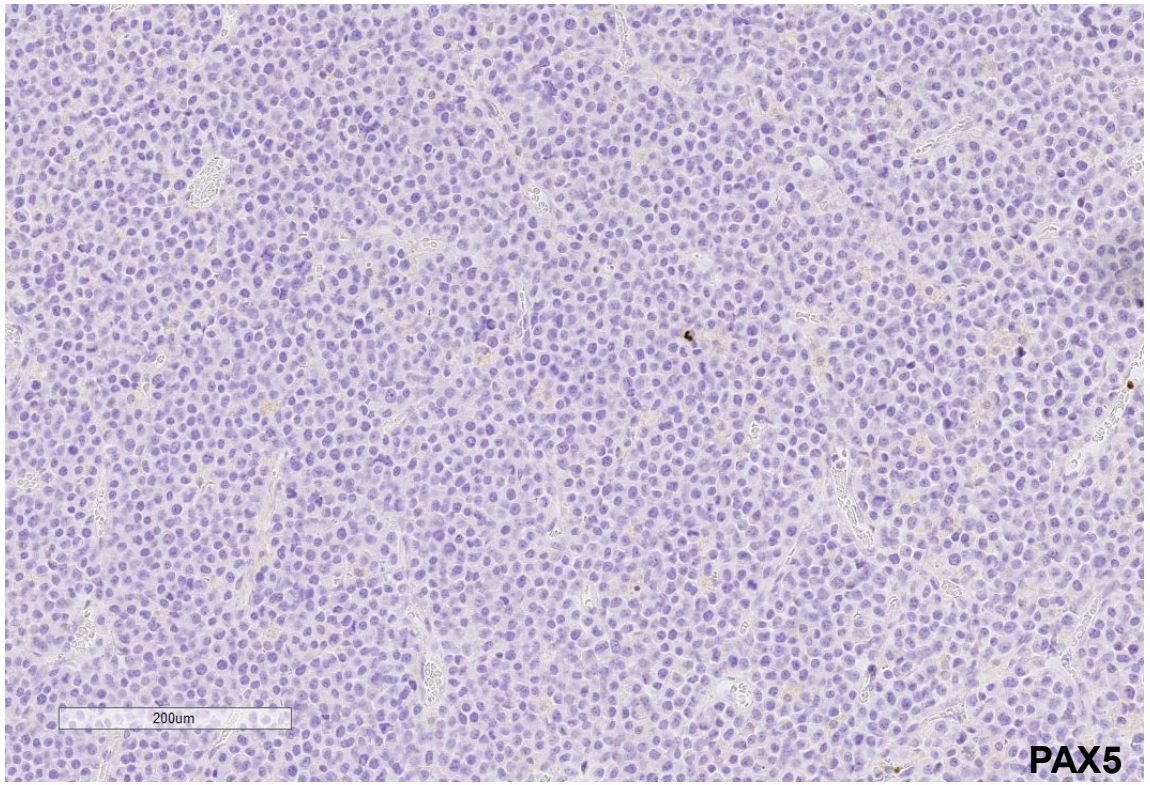


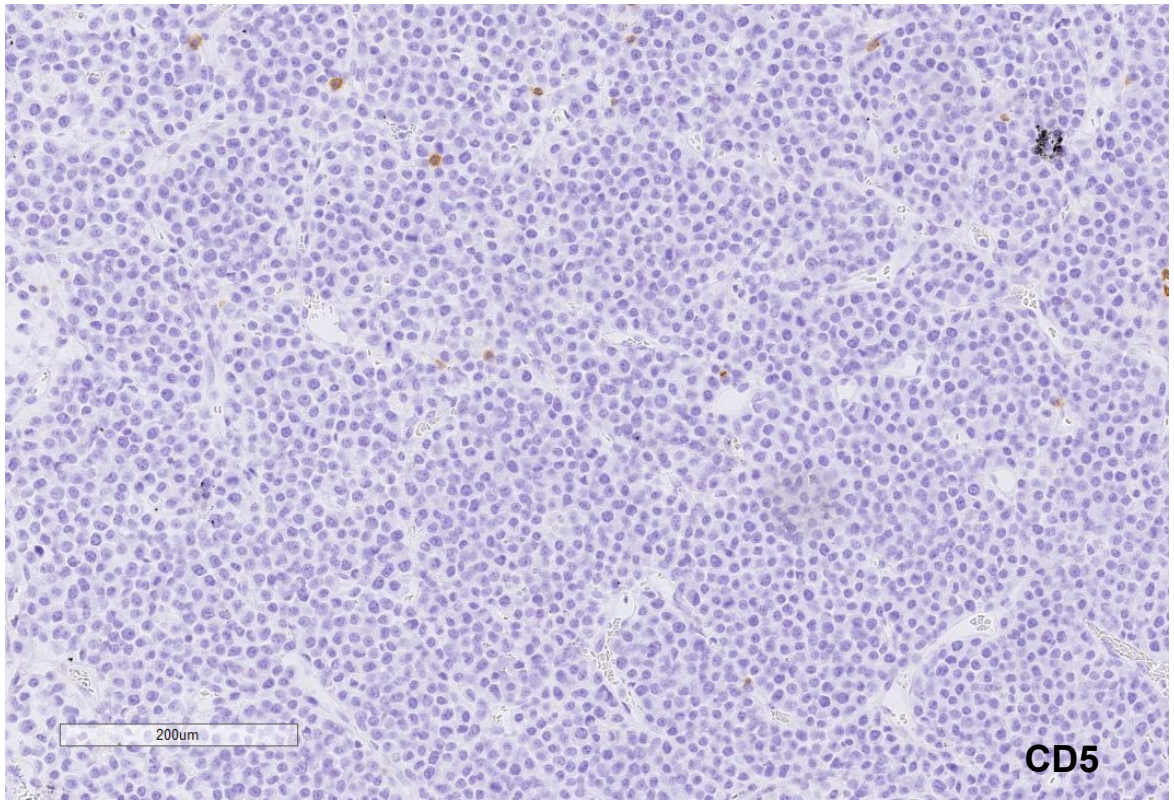
nn Medicine



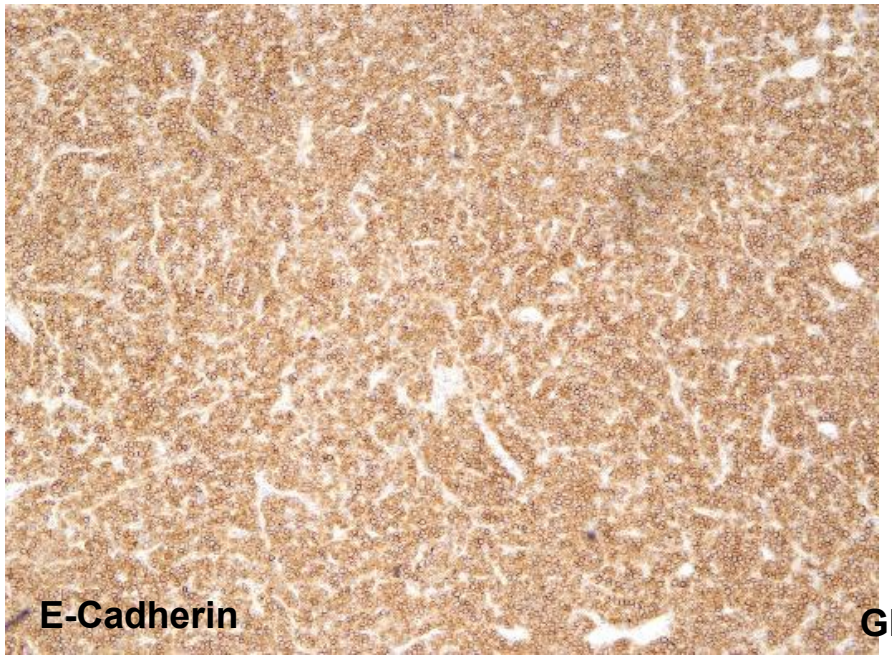
Leukosialin (CD43) defines hematopoietic progenitors

Penn Medicine

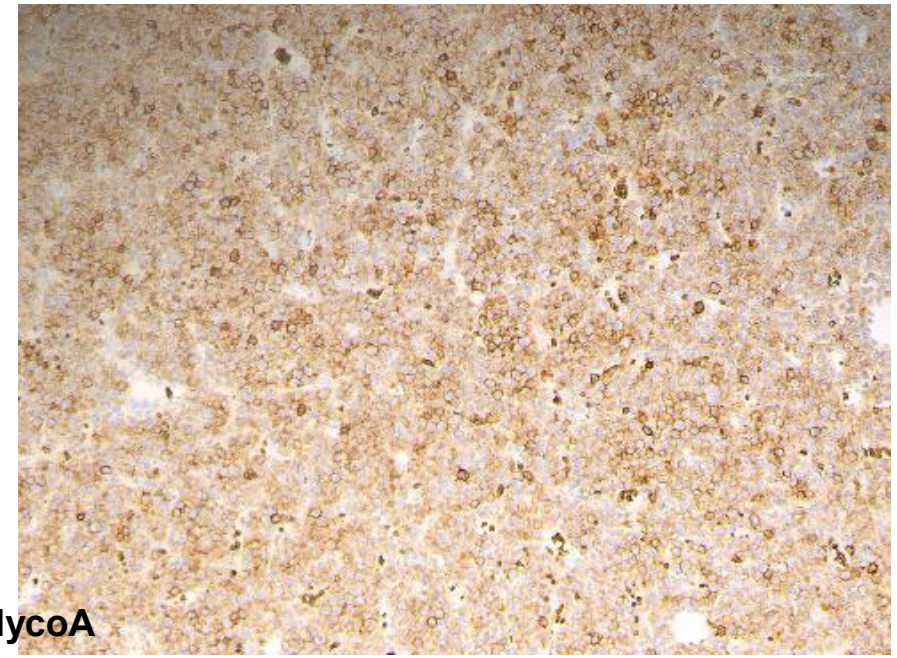




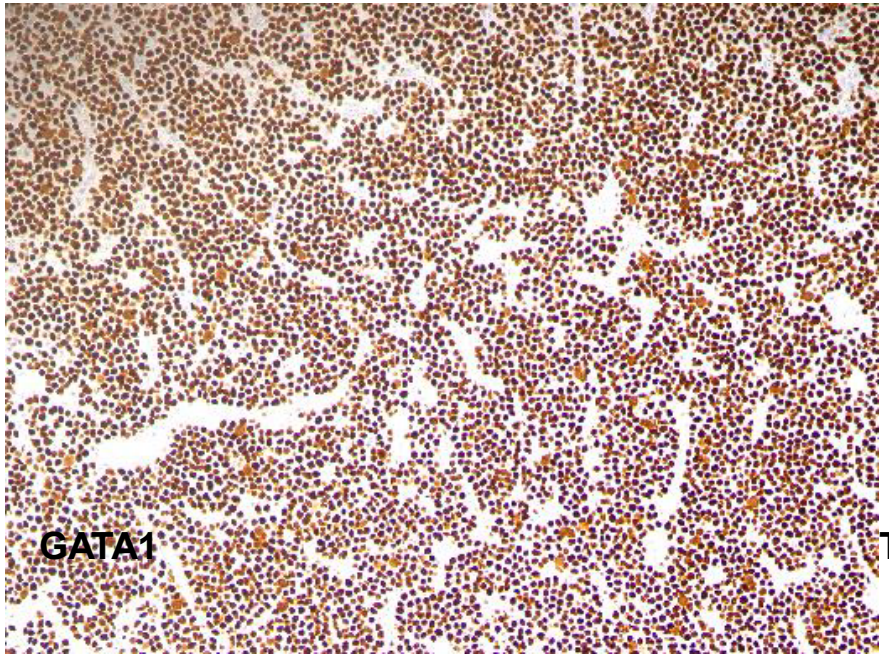
Penn Medicine



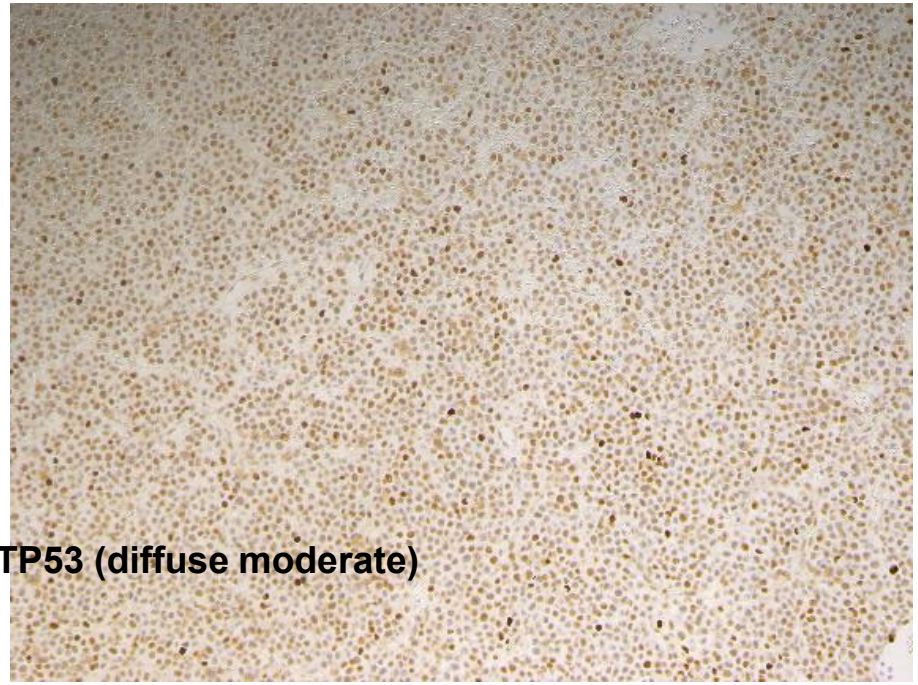
E-Cadherin



GlycoA



GATA1



TP53 (diffuse moderate)

Penn Medicine

Final Diagnosis

Erythroid sarcoma/Erythroblastic Sarcoma

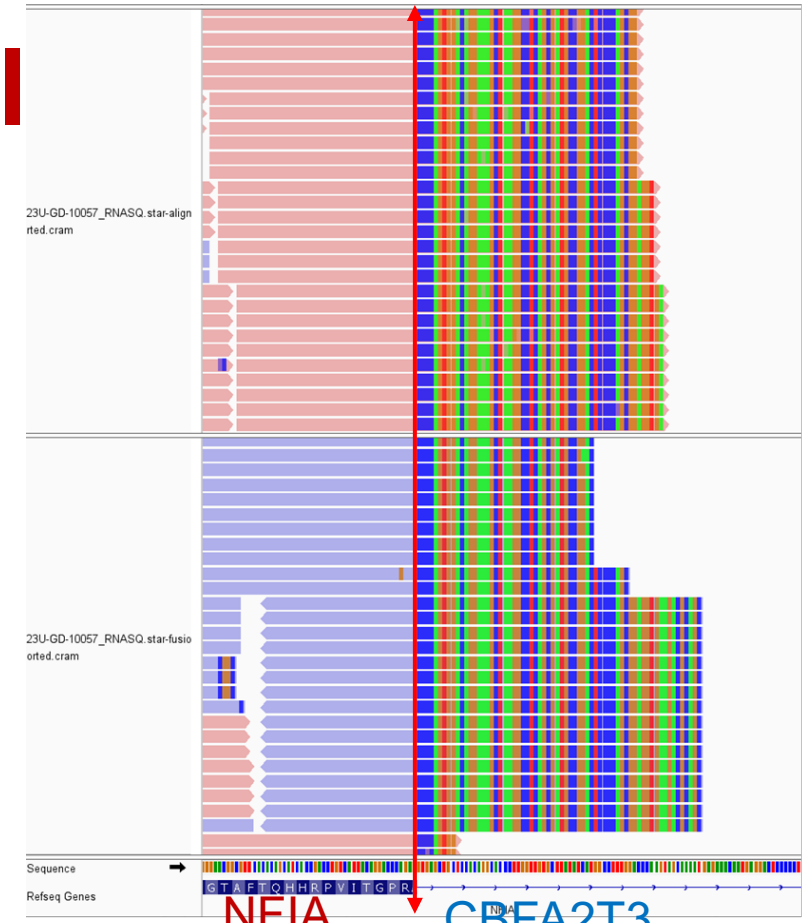
Subsequent Bone Marrow Biopsy: Trilineage hematopoiesis, negative for involvement

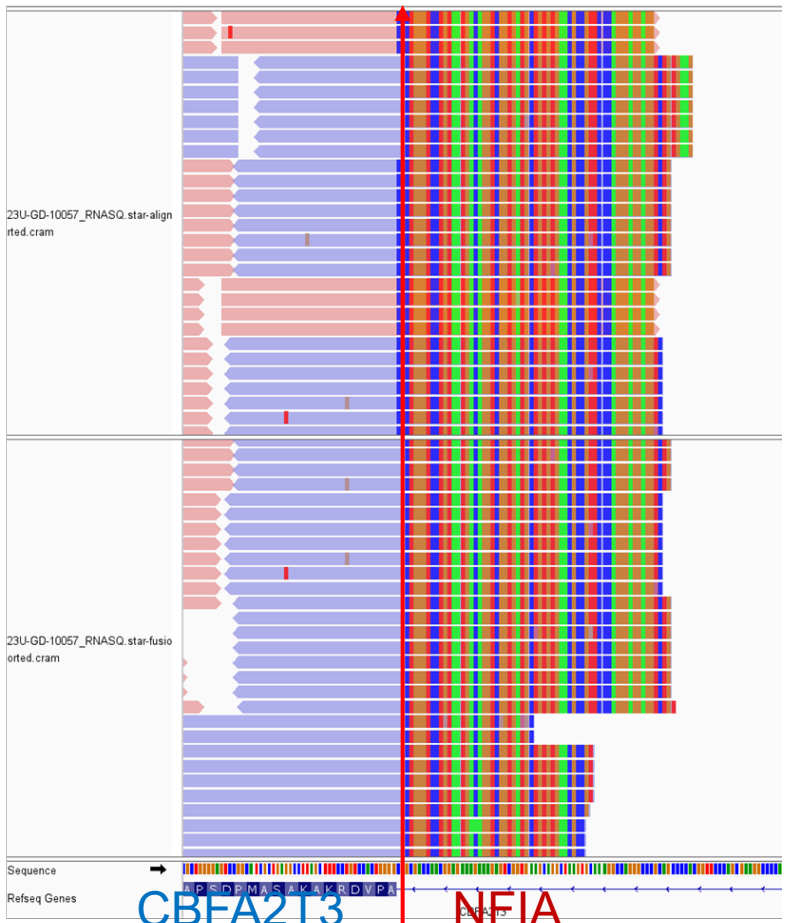
Penn Medicine

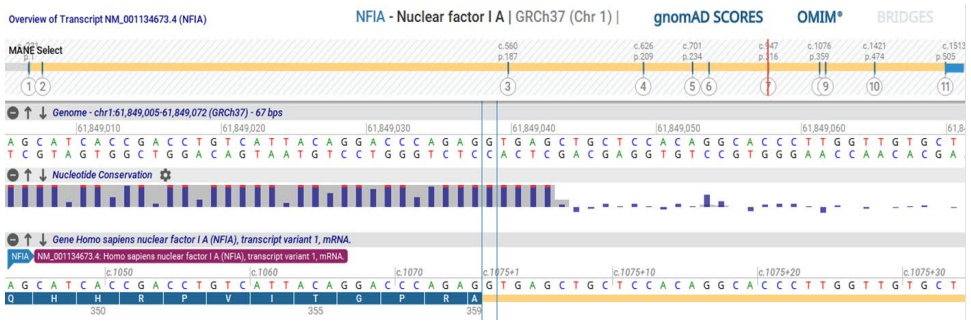
RNA Seq Resul

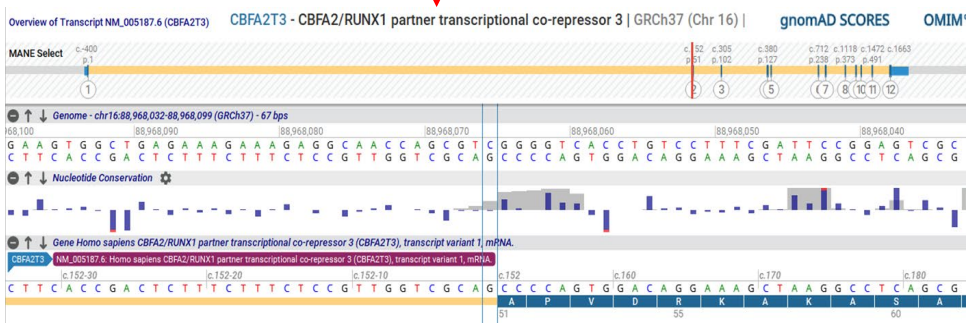
***NFIA*(NM_001134673.4)::*CBFA2T3*(NM_005187.6)**

Pure CNS Erythroid Sarcoma with NFIA::CBFA2T3 Fusion









Penn Medicine

Classification
[Leukemia: Bone Marrow & Blood Involvement]
[Sarcoma: Extramedullary/Tissue Involvement]

First described in 1917 and named after Giovanni DiGuglielmo, ~~FAB M6 1976~~

2001 WHO included this entity as M6a (acute erythroid/myeloid leukemia) and M6b (acute erythroid leukemia)

WHO 2016 & 2022
AML defined by differentiation

Acute/Pure Erythroid Leukemia (AEL/PEL)

ICC 2022

Acute Myeloid Leukemia with mutated *TP53* *(with an optional comment on its erythroid differentiation)*

Essential: erythroid predominance, usually ≥ 80% of bone marrow elements, of which ≥ 30% are proerythroblasts.

Desirable: evidence of *TP53* mutation.

Penn Medicine

Adult predominant PEL – TP53 driven

- Biallelic TP53 inactivation (two hits via mutation/LOH/17p loss) underlies most adult PEL
- Overrides PEL label and move to AML with TP53

- Complex karyotype (100%)
- Del of 17p (95%)
- Monosomal Karyotype (90%)
- Abnormalities of 5/5q (78%)
- Abnormalities of 7/7q (66%)

Pure erythroid leukemia is characterized by biallelic *TP53* inactivation and abnormal p53 expression patterns in *de novo* and secondary cases

Hong Fang [1], Sa A Wang [1], Joseph D Khoury [1], Siba El Hussein [1], Do Hwan Kim [1], Mehrnoosh Tashakori [1], Zhenya Tang [1], Shaoying Li [1], Zhihong Hu [2], Fatima Zahra Jelloul [1], Keyur P Patel [1], Timothy J McDonnell [1], Tapan Kadia [3], L Jeffrey Medeiros [1], Wei Wang [1,✉]

Genomic landscape of *TP53*-mutated myeloid malignancies

Haley J Abel [1], Karolyn A Oetjen [1], Christopher A Miller [1], Sai M Ramakrishnan [1], Ryan B Day [1], Nichole M Helton [1], Catrina C Fronick [2], Robert S Fulton [2], Sharon E Heath [1], Stefan P Tarnawsky [1], Sridhar Nonavinkere Srivatsan [1], Eric J Duncavage [3], Molly C Schroeder [3], Jacqueline E Payton [3], David H Spencer [1,2,3], Matthew J Walter [1], Peter Westervelt [1], John F DiPersio [1], Timothy J Ley [1], Daniel C Link [1,*]

Clinical, Morphologic, and Cytogenetic Characteristics of 26 Patients With Acute Erythroblastic Leukemia

By Olufunmilayo I. Olopade, Maya Thangavelu, Richard A. Larson, Rosemarie Mick, Areta Kowal-Vern, Harold R. Schumacher, Michelle M. Le Beau, James W. Vardiman, and Janet D. Rowley

Pediatric/infant PEL: TP53-wt enriched for NUP98 fusion

Rare and aggressive subtype of AML

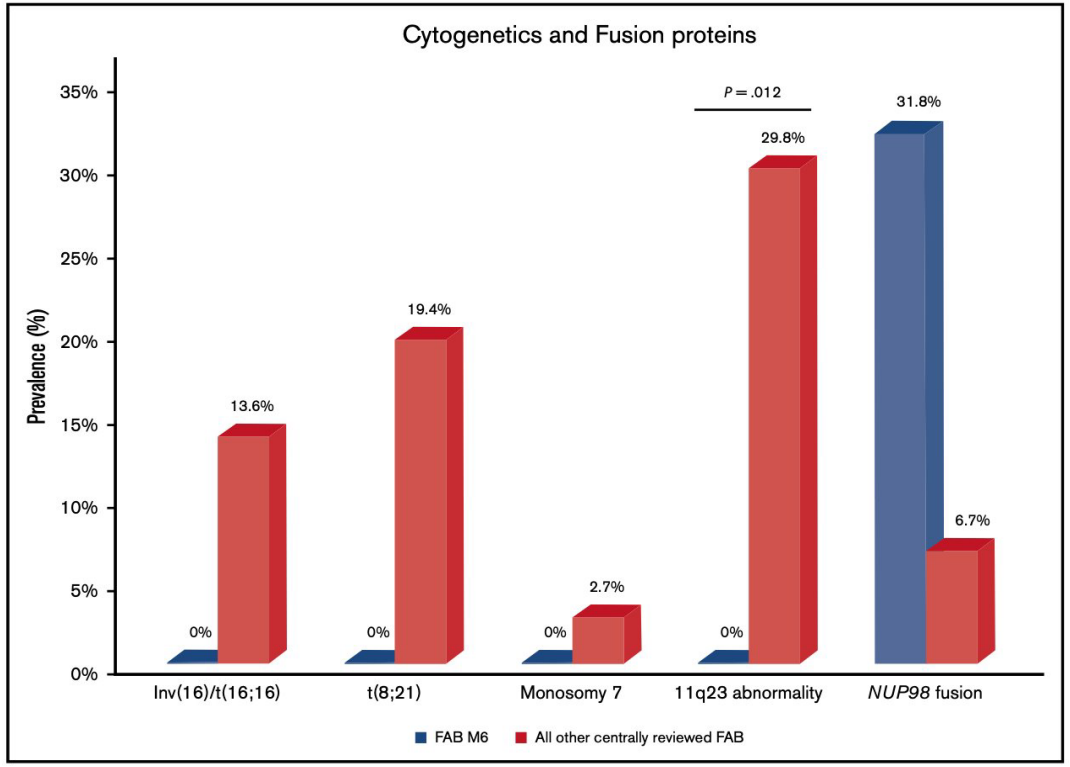
24 cases from database
5 had a pure erythroid phenotype
19 had an erythroid/myeloid phenotype

- NUP98 fusions were highly enriched in patients with AEL, occurring in 7 of 22 cases for which molecular data were available
- Of 5 cases of pure erythroid leukemias (PELs), 3 had NUP98 fusions, and 4 had complex karyotypes (trisomy 6, 8, and 21 seen).
  - Notably **NUP98::KDM5A and NUP98::NSD1**
- AEL is a morphologically and genetically heterogeneous entity that is enriched in NUP98 fusions, with the pure erythroid subtype associated with particularly adverse outcomes and high chances of relapse.

Acute erythroid leukemia is enriched in *NUP98* fusions: a report from the Children's Oncology Group

Karen M. Chisholm,[1,2] Amy E. Heerema-McKenney,[3] John K. Choi,[4] Jenny Smith,[5] Rhonda E. Ries,[5] Betsy A. Hirsch,[6] Susana C. Raimondi,[4] Todd A. Alonzo,[7] Yi-Cheng Wang,[8] Richard Aplenc,[9] Lillian Sung,[10] Alan S. Gamis,[11] Soheil Meshinchi,[5] and Samir B. Kahwash[12]

[1]Department of Laboratories, Seattle Children's Hospital, Seattle, WA; [2]Department of Laboratory Medicine and Pathology, University of Washington Medical Center, Seattle, WA; [3]Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH; [4]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL; [5]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [6]Division of Laboratory Medicine, University of Minnesota Medical Center, Fairview, Minneapolis, MN; [7]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA; [8]Children's Oncology Group, Monrovia, CA; [9]Children's Hospital of Philadelphia, Philadelphia, PA; [10]Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada; [11]Children's Mercy Hospitals & Clinics, Kansas City, MO; and [12]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, OH



Penn Medicine

Other rare TP53-negative but genetically distinct uncommon, most in neonates/young children, isolated extramedullary disease

- CIC rearrangements (**CIC::NUTM2A)**
  - Infant with isolated myeloid sarcoma with negative marrow involvement by flow
  - Sequencing shows CIC-NUTM2A fusion in marrow despite no pathlogy -> myeloid sarcoma clonally evolved from bone marrow
- NFIA partner fusion (ETO family)
  - NFIA::RUNX1T1 (ETO1)
    - Pediatric CNS erythroid sarcoma; often CNS-tropic
  - NFIA::CBFA2Te (ETO2)
    - Similar biology
    - Reported co-lesions: EPOR, JAK2, ARID1A

Malignant Progression of an Ancestral Bone Marrow Clone Harboring a CIC–NUTM2A Fusion in Isolated Myeloid Sarcoma

Jennifer L Kamens [1], Jinjun Dang [1], Timothy I Shaw [2], Alexander M Gout [3], Scott Newman [3], Kohei Hagiwara [3], Amelia M R Smith [1], Alyssa N Obermayer [2], Sarah Aldridge [4], Jing Ma [5], Yang Zhang [6], Gang Wu [7], Vasiliki Leventaki [8], Teresa Santiago [5], Susana Raimondi [5], Joy Nakitandwe [9], Alberto Pappo [4], Chunliang Li [6], Jinghui Zhang [3], Tanja A Gruber [1]

CNS erythroblastic sarcoma: a potential emerging pediatric tumor type characterized by NFIA::RUNX1T1/3 fusions

Arnault Tauziède-Espariat [# 1 2], Lucille Lew-Derivry [3], Samuel Abbou [4], Alice Métais [# 5 6], Gaëlle Pierron [7 8], Stéphanie Reynaud [8], Julien Masliah-Planchon [8], Cassandra Mariet [5], Lauren Hasty [5], Volodia Dangouloff-Ros [9 10], Nathalie Boddaert [9 10], Marie Csanyi [11], Aude Aline-Fardin [12], Claire Lamaison [13], Fabrice Chrétien [5], Kévin Beccaria [14], Stéphanie Puget [15], Pascale Varlet [5 6]

***De novo* primary central nervous system pure erythroid leukemia/sarcoma with t(1;16)(p31;q24) *NFIA/CBFA2T3* translocation**

Penn Medicine

Penn Medicine