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Multi-Institutional Hematopathology Interesting Case Conference

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Clinical Information

- 12-year-old male with autism
- Nine-month history of daily headaches with photophobia, ataxia, and thirty-pound weight loss
- Initial workup:
  - -Peripheral blood eosinophilia
  - -Lumbar puncture: Elevated opening pressure (36mm H2O)
- MRI of brain and spine showed diffuse leptomeningeal enhancement
- Three brain biopsies: mixed inflammatory infiltrate with eosinophilia
- Empiric treatment with steroids and IVIG →failed to improve headaches and ataxia
- Discharged for outpatient follow up

	Reference range	Patient (Presentation #1)
Protein (mg/dl)	15-40	238
Glucose (mg/dl)	40-70	51
Cytokine levels (sIL2r, IL-6, IL-10)	sIL2r < 26.8 IL-6 < 7.5 IL-10 < 12.7	sIL2r = 13,780 IL-6 = 340.5 IL-10 = 1,068.7
Cell count (/cumm)	0-5	18 (ref: 0-5/cumm)

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Clinical Information – contin'd

- Nine months after initial presentation → increasing somnolence, worsening ataxia, new vomiting episodes
- MRI: worsened leptomeningeal enhancement
- Admitted for brain biopsy
- Peripheral blood flow cytometry and bone marrow were negative, and no evidence of disease was identified outside the CNS

	Patient (Presentation #2)
Protein (mg/dl)	380 (ref: 15-40 mg/dl)
Glucose (mg/dl)	52 (ref: 40-70 mg/dl)
Cytokine levels (sIL2r, IL-6, IL-10)	sIL2r = 39,485 (ref: <26.8) IL-6 = 2,436 (ref: <7.5) IL-10 = 42,731 (ref: <12.7)
Cell count (/cumm)	29 (ref: 0-5/cumm)

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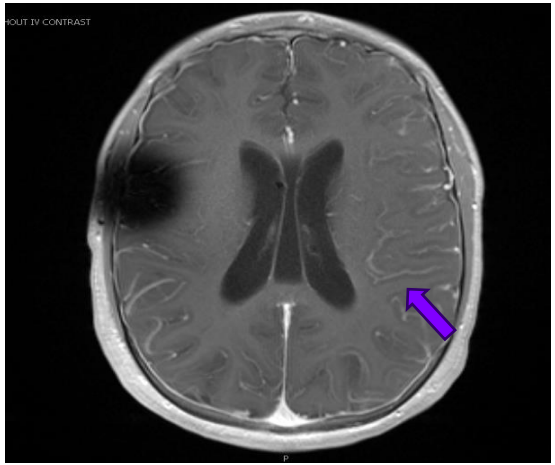
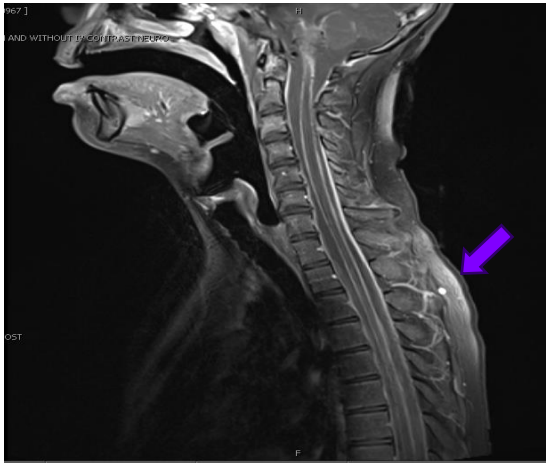
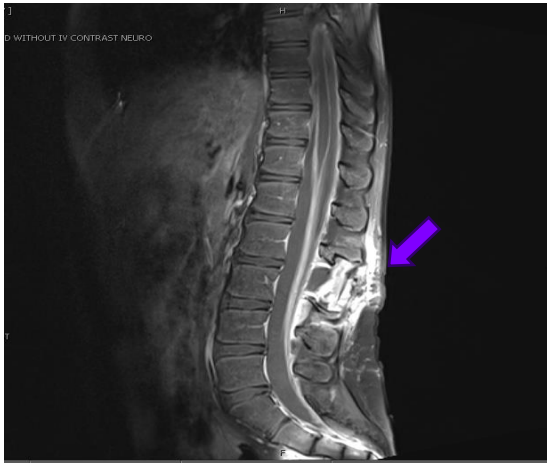
Clinical Information – Imaging



- Brain MRI: diffuse leptomeningeal enhancement
  (T1 post-contrast)





- Spine MRI: diffuse leptomeningeal enhancement
  (T1 fat-saturated post-contrast)

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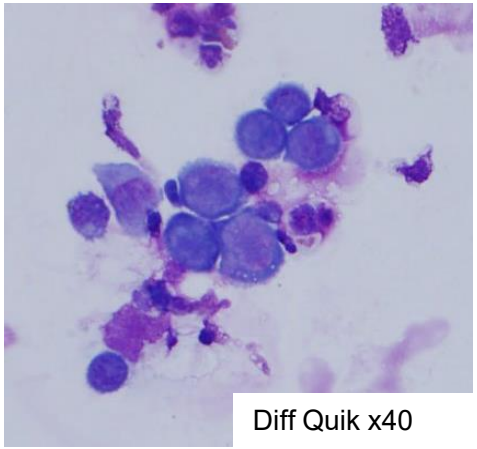
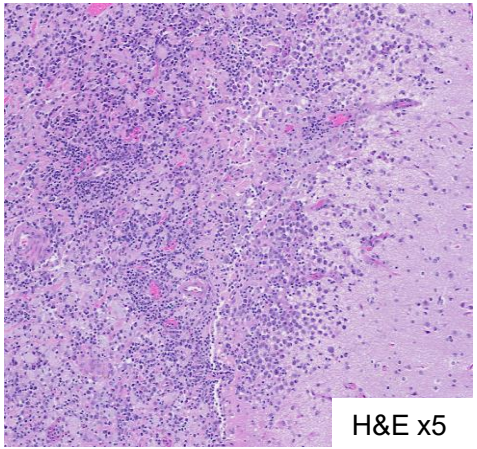
Details of Microscopic Findings



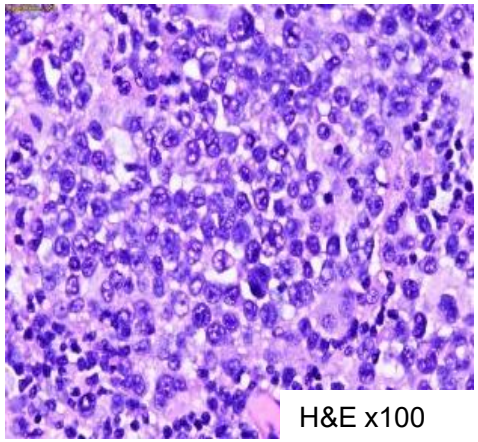
Diff Quik x40

- CSF cytology: Immature malignant cells with fine chromatin, high nucleus to cytoplasmic ratios and prominent nucleoli



H&E x5

- Predominantly dural based, the atypical cells formed clusters and extended into the brain parenchyma against a background of significant mixed inflammation



H&E x100

- Brain nodule biopsy: Focal infiltration by atypical immature mononuclear cells with marked pleomorphism

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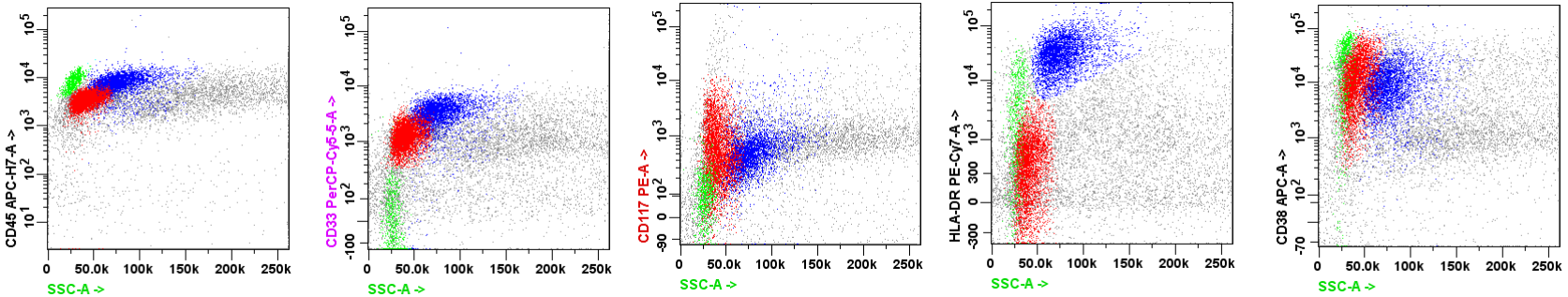
Immunophenotype

- Flow cytometric analysis of CSF: CD45, CD33, CD117, CD38 positive large cells



Red = Population of interest
Blue = Monocytes
Green = Lymphocytes

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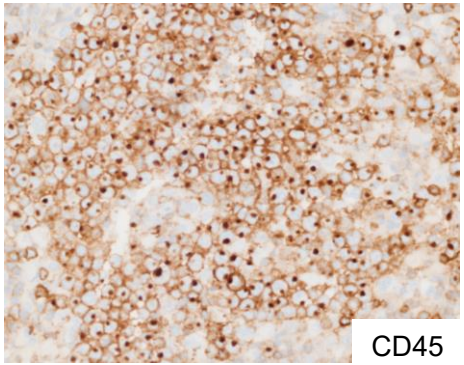
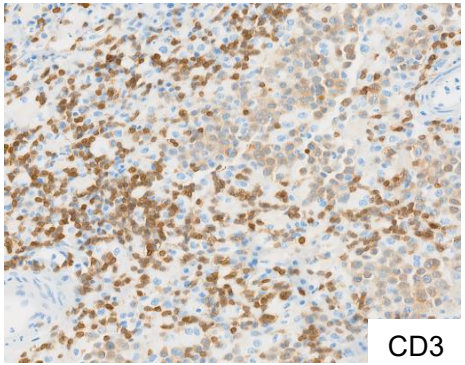
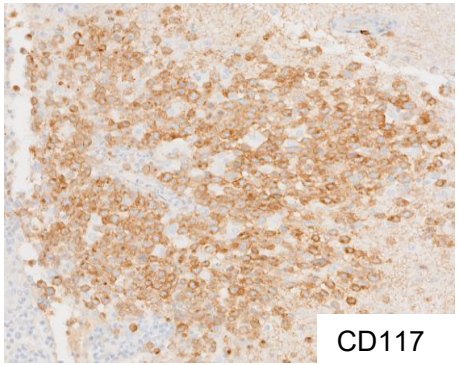
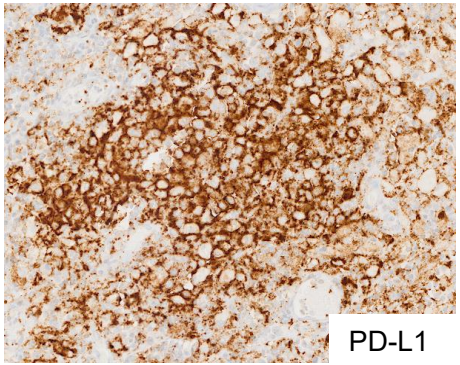
Immunophenotype

Markers	Expression
CD45	+ (prominent golgi staining pattern)
CD3	+ (weak, cytoplasmic)
CD43	+
CD7	+
CD117	+
PDL-1	+


CD45


CD3


CD117


PD-L1

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Immunophenotype

Markers	Expression
CD34	-
CD4	-
CD8	-
CD5	-
MPO	-
MUM1	-
PAX5	-

Markers	Expression
CD123	-
CD14	-
CD33	-
CD2	-
ALK	-
TdT	-
EMA	-

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Molecular Studies

- Next generation sequencing identified a ***SMARCB1*c.140_141insA p.Y47fs*1** frameshift variant at 2.3% variant allele frequency (VAF)
- No other reportable genomic alterations were detected

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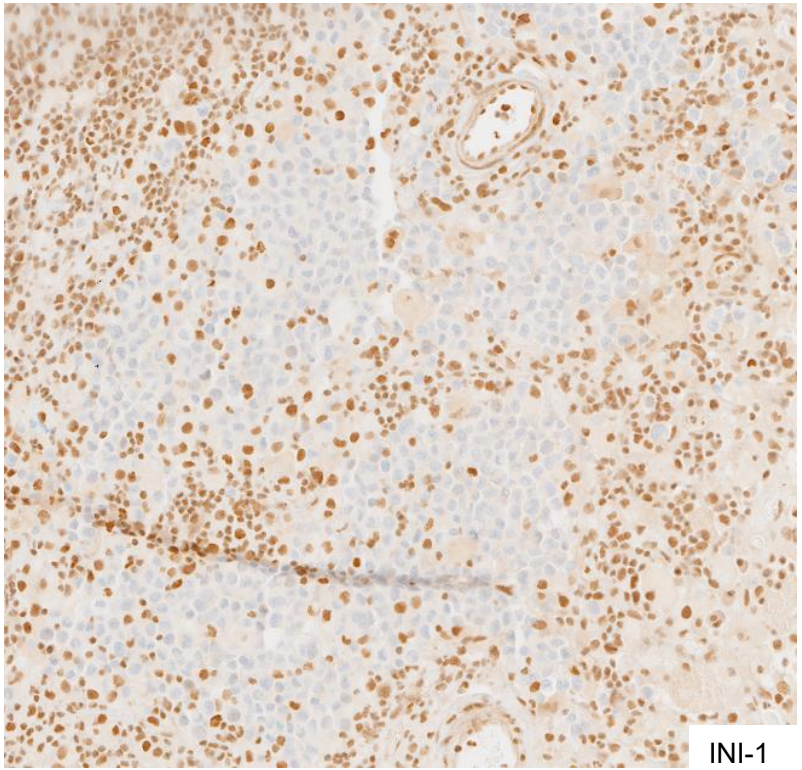
Immunophenotype

Markers	Expression
INI-1	-



INI-1

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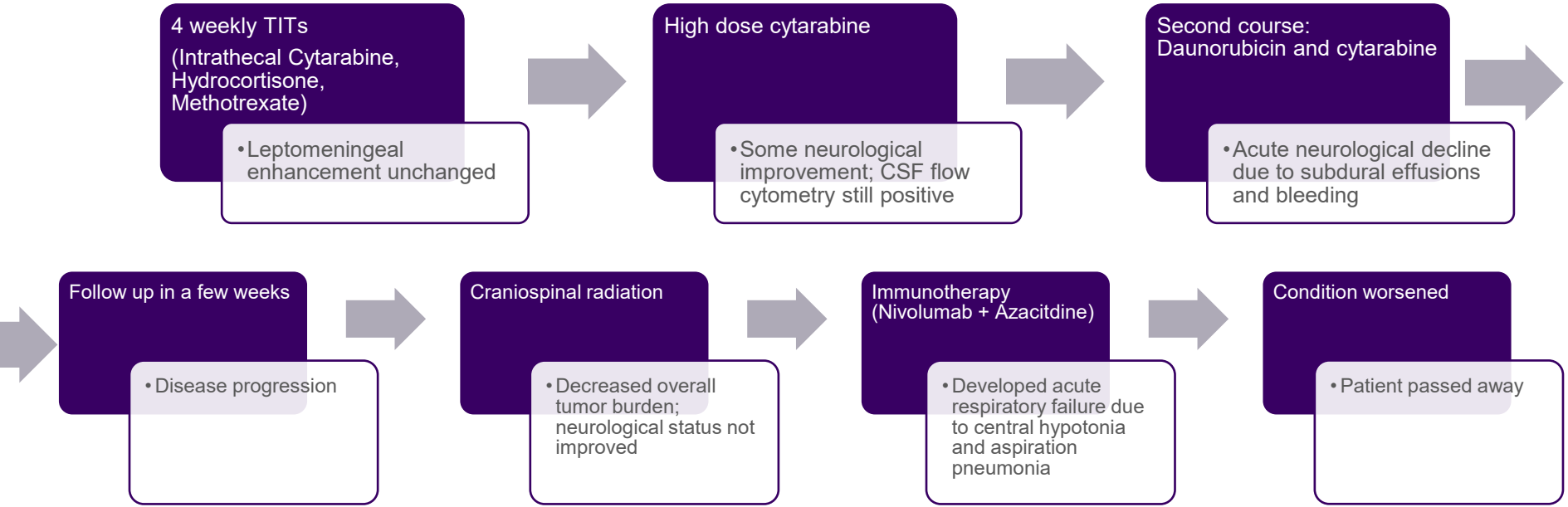
Treatment and Course



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Diagnosis

Hematopoietic neoplasm with T-cell phenotype and loss of *SMARCB1* (INI-1) expression

Or

SMARCB1-deficient hematolymphoid neoplasm

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Current Understanding of *SMARCB1* in Hematolymphoid Neoplasms

- Also known as INI1, *SNF5*, or BAF47
- Tumor suppressor gene encoding a subunit of the SWI/SNF chromatin-remodeling complex
- Regulates transcription, cell differentiation, and proliferation
- Well studied in aggressive solid tumors (malignant rhabdoid tumor, renal medullary carcinoma, epithelioid sarcoma, etc.)
- Role in hematolymphoid malignancies is emerging; there is limited but growing body of evidence

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Key reported cases in the current literature

Authors	Patient characteristics	Clinical presentation	Immunophenotype	Diagnosis
Kinnaman et al	14-year-old male with autism spectrum disorder	Mediastinal mass, lymphadenopathy	CD45, CD2, CD7, CD79a, MPO (dim), CD13	Malignant hematopoetic neoplasm with T/NK cell, B cell, and myeloid differentiation and biallelic *SMARCB1* loss
Havens et al	6-year-old male with distal chromosome 22q11.2 microdeletion syndrome	Back and vertebral lesions	CD2, CD3, CD5, CD4 (weak), CD45, CD43	INI-1 deficient hematolymphoid neoplasm
Havens et al	11-year-old male	Mediastinal mass	CD45, CD4, CD7, CD30 focal	INI-1 deficient hematolymphoid neoplasm
Havens et al	9-year-old male	Mediastinal mass, dyspnea, pleural effusion	CD45, CD43, CD5, CD4 (patchy), CD30 (patchy)	INI-1 deficient hematolymphoid neoplasm
Sarami et al	67-year-old female	Right lower extremity mass, night sweats, weight loss	CD45, CD43, CD7, CD33	Hematolymphoid neoplasm with *SMARCB1* loss

Experimental evidence

- Fischer et al analyzed a cohort of 315 mature T-cell lymphoma cases to see how *SMARCB1* behaves across subtypes
- Key findings:

1. ***SMARCB1* expression is heterogenous**
    - Most cases expressed SMARCB1, but a subset had complete loss
    - Loss was enriched in pediatric cases, especially within Peripheral T-cell lymphoma, not otherwise specified
2. **Link to tumor microenvironment (TME)**
    - Tumors without SMARCB1 had an immunosuppressive microenvironment (↓ T/NK cells, ↑ Myeloid-derived suppressor cells)
3. **Therapeutic implications**
    - Histone deacetylase (HDAC) inhibitor (SAHA - suberoylanilide hydroxamic acid) mimicked SMARCB1 re-expression in *SMARCB1*-deficient PTCL-NOS cells
    - Combine with immune checkpoint blockade (eg. Anti-PD1) to reverse TME suppression

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Pathogenesis and potential targets

- Loss of *SMARCB1* → dysregulated chromatin structure → altered gene expression
- Mechanism:
  - Loss leads to upregulation of Polycomb Repressor Complex 2 (PRC2) activity
  - PRC2 catalytic subunit EZH2 → trimethylates histone 3 (H3K27me3) → gene repression
- Result: Blocked differentiation, uncontrolled proliferation, and immune evasion

Target	Rationale	Therapy Example
PRC2/EZH2	Overactive in *SMARCB1* loss	Tazemetostat (EZH2 inhibitor)
EED (PRC2 component)	Required for PRC2 function	Experimental EED inhibitors
Histone deactylases (HDACs)	HDAC inhibition mimics *SMARCB1* re-expression	SAHA / Vorinostat
Immune checkpoints	TME shows immune suppression	Anti-PD-1/Anti-PD-L1

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Key takeaways: Our Case in Context

- Novelty & Significance:
  - First reported case of *SMARCB1*-deficient hematolymphoid neoplasm with isolated central nervous system involvement (no systemic disease or marrow involvement)
  - Unusual presentation: insidious eosinophilic meningitis with progressive mental status decline, prolonged course, and marked inflammatory response
  - INI-1 loss raises questions about molecular drivers and disease classification
  - PD-L1 positivity indicates an immunosuppressive tumor microenvironment that may facilitate immune evasion
  - Expands the anatomical and biological spectrum of this rare entity

- Clinical & Research Implications:
  - Discussion point: **When should INI-1 staining be considered in hematolymphoid cases?**
  - Further studies are needed to determine whether SMARCB1-negative PTCL-NOS represents a distinct molecular subtype
  - Recognizing and characterizing SMARCB1-deficient neoplasms is crucial, as these rare molecular aberrations may reveal actionable alterations and inform targeted therapeutic strategies

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Thank you

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