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Multi-Institutional Hematopathology Interesting Case Conference

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Hematopathology Fellow (PGY-5)

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Department of Pathology

Clinical Presentation

- 73-year-old female with no significant past medical history
- Presented to the ED due to a syncopal episode
  - Febrile (102.2 F), tachycardic and intermittent hypotension
- Prior to the episode, complained of 1 week of chest discomfort, poor appetite and reduced fluid consumption

Test	Result	Reference Range
Hemoglobin	**8.3 g/dL**	11.2 – 15.7 g/dL
Hematocrit	**25%**	34 – 45%
WBC	**1.6 /µL**	4.0 – 10.0 /µL
Platelet Count	**49,000 /µL**	150 – 400 /µL
Ferritin	**2,957 ng/mL**	12 – 204 ng/mL
Triglycerides	**235 mg/dL**	0 – 149 mg/dL
Fibrinogen	**137 mg/dL**	150 – 450 mg/dL

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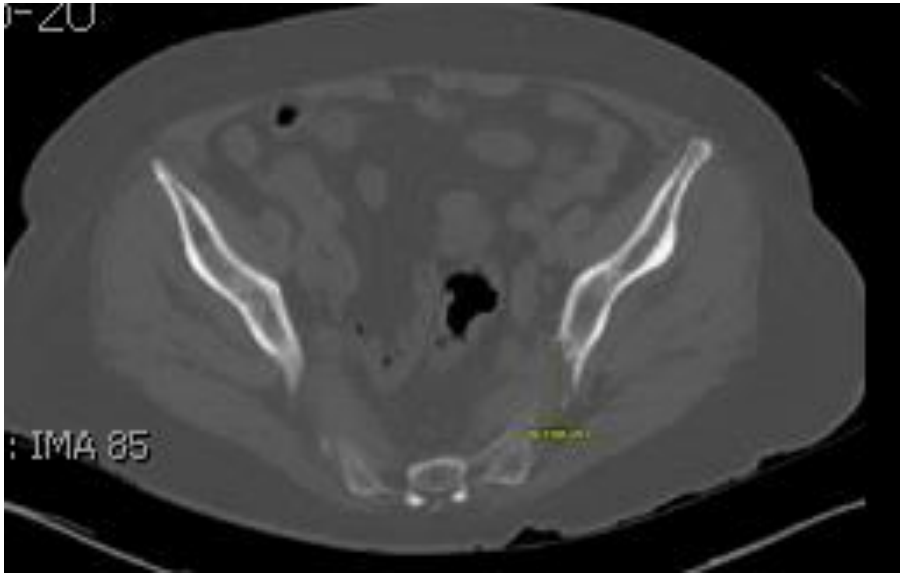
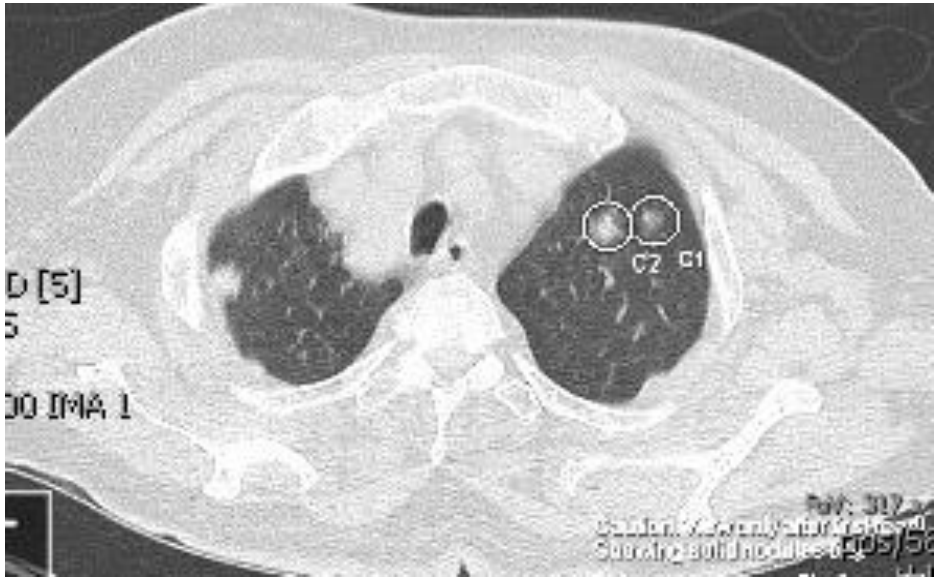
Imaging

CT: Abdomen



Shows a left iliac cystic lesion concerning for metastatic disease.

CT: Chest



Multiple nodules concerning for metastatic disease vs infection vs inflammation.

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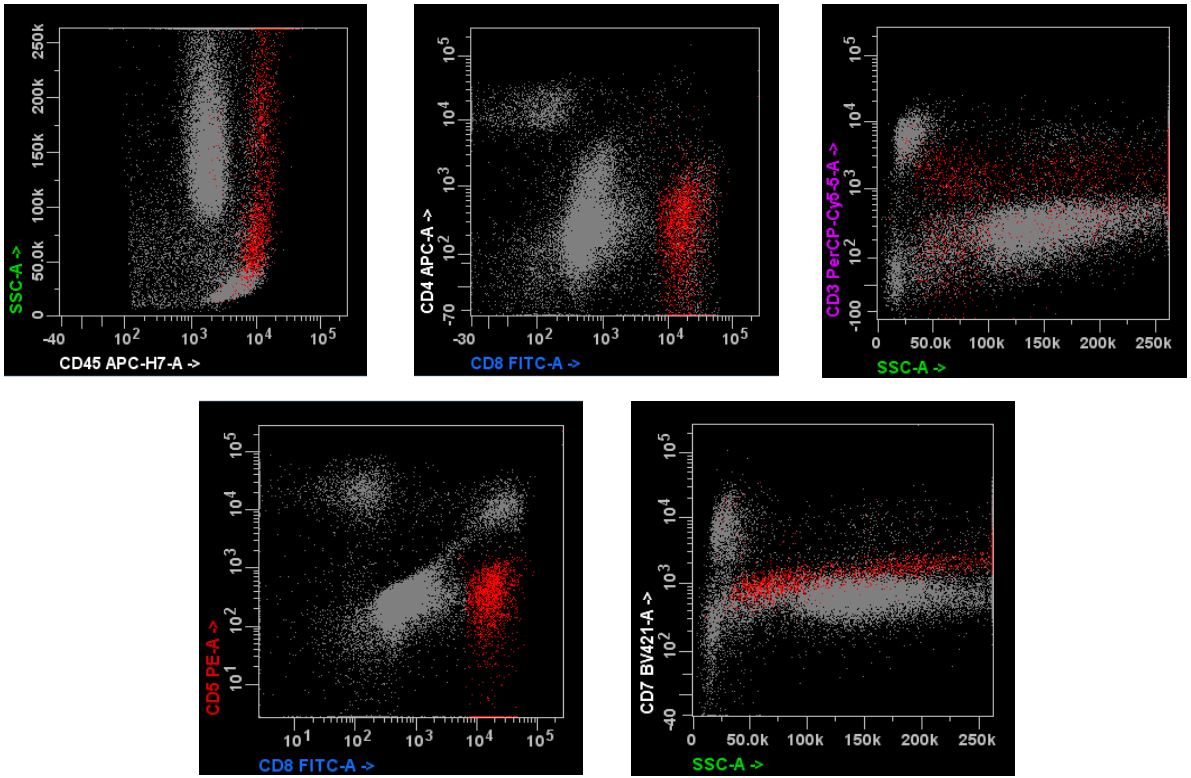
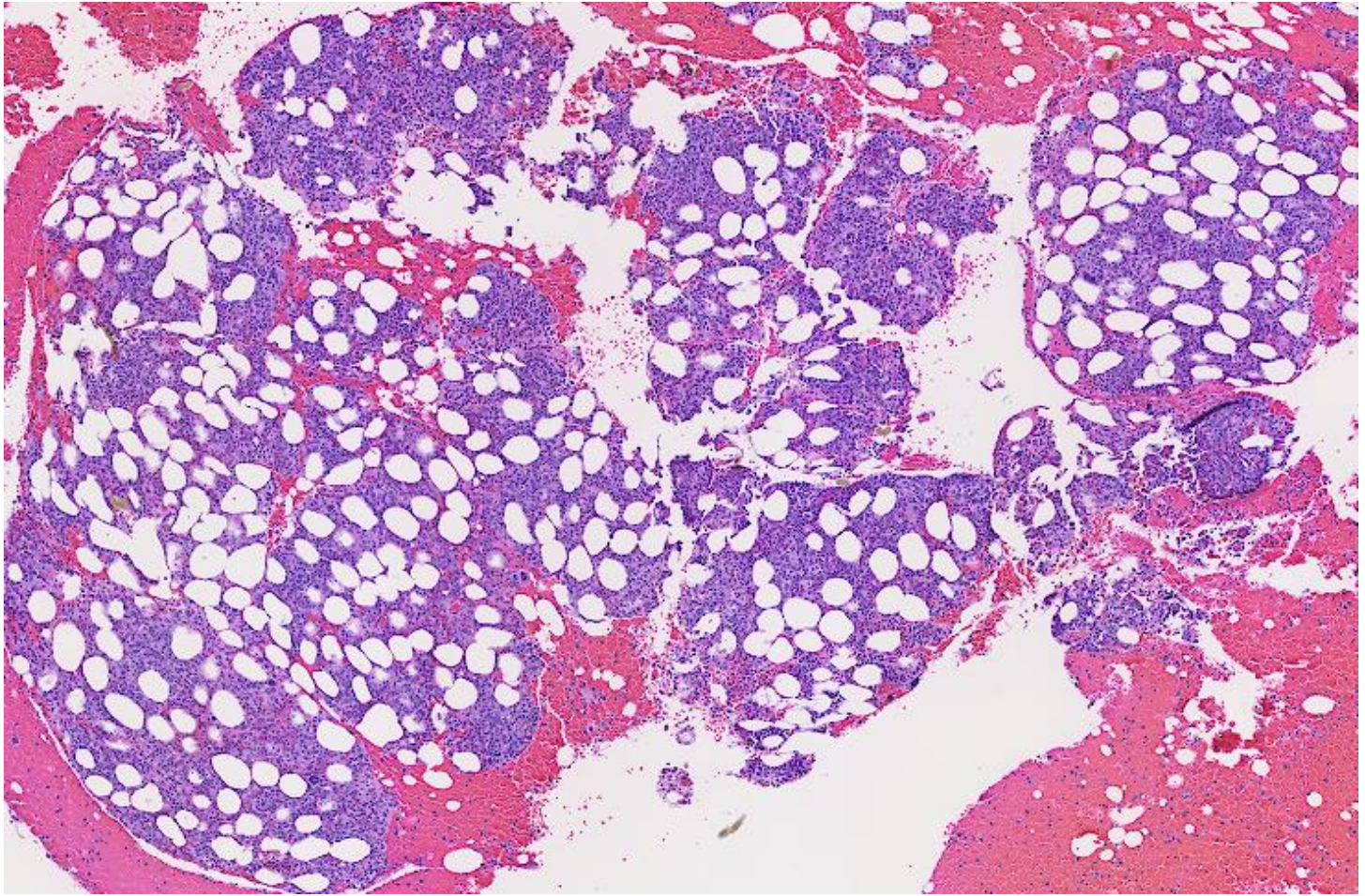
Flow Cytometry



Immunophenotype:
6.7% cells with the following immunophenotype: CD45(+), CD3 (subset+; 50%), CD8(+), CD4(-), CD2(+), CD5(-), CD7(-), CD38(+), CD56(-), TCRab(+) and TCRgd(-).

Hypercellular marrow (50-60% cellularity)



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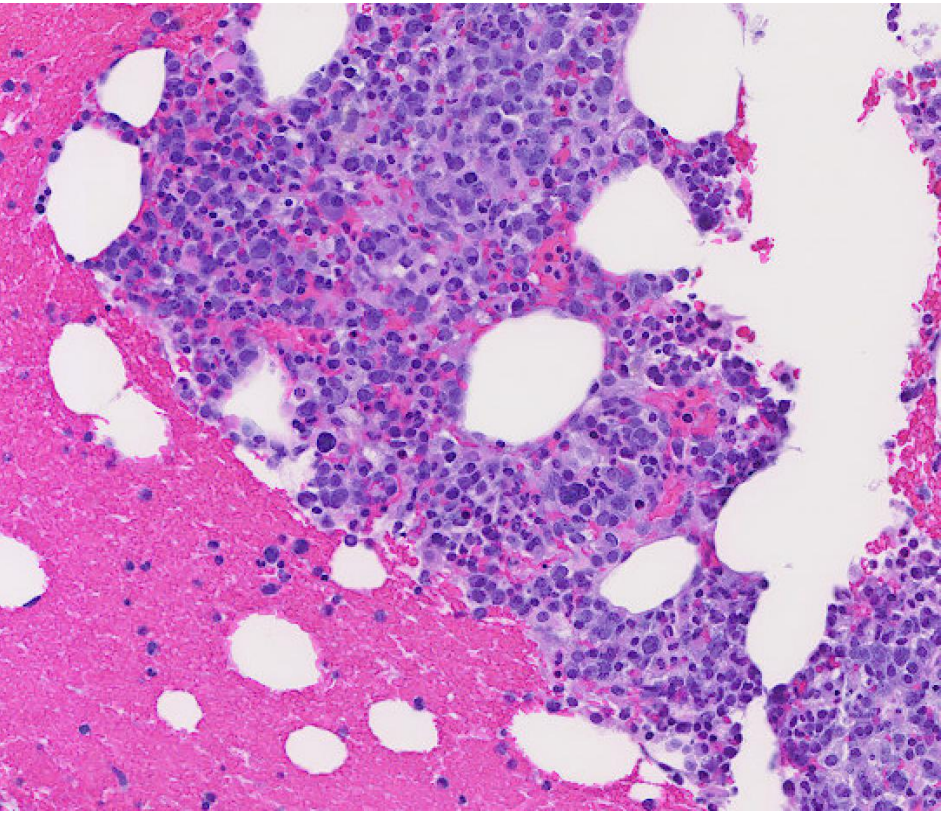

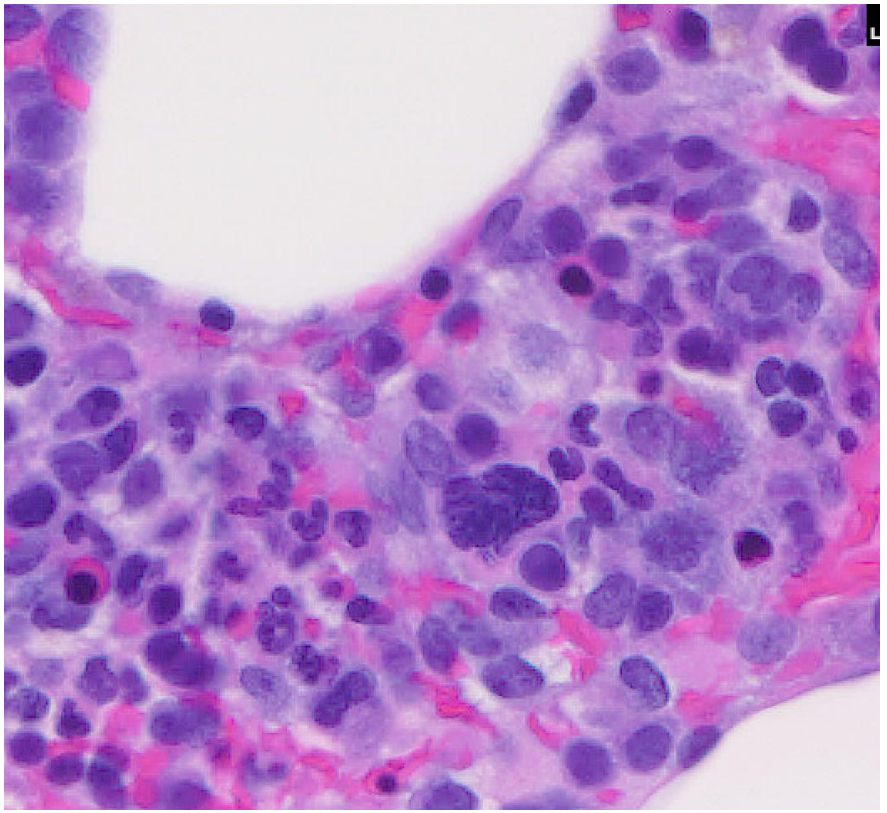

Scattered large pleomorphic cells in a background of small lymphocytes, plasma cells and histiocytes.

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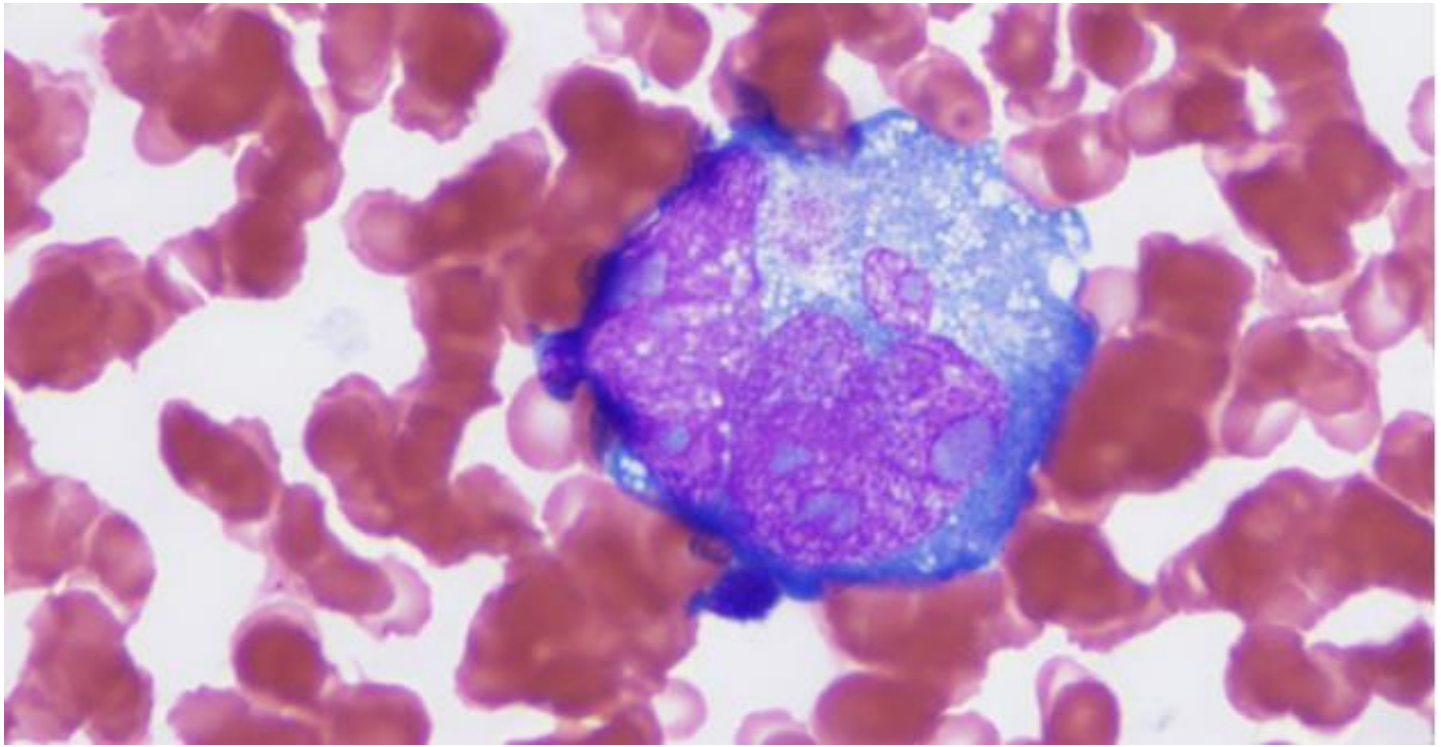
Aspirate smear



- Pleomorphic large cells with accentuated membranes, basophilic cytoplasm and prominent nucleoli
  - Often bi-lobed to multi-lobated nuclei were seen

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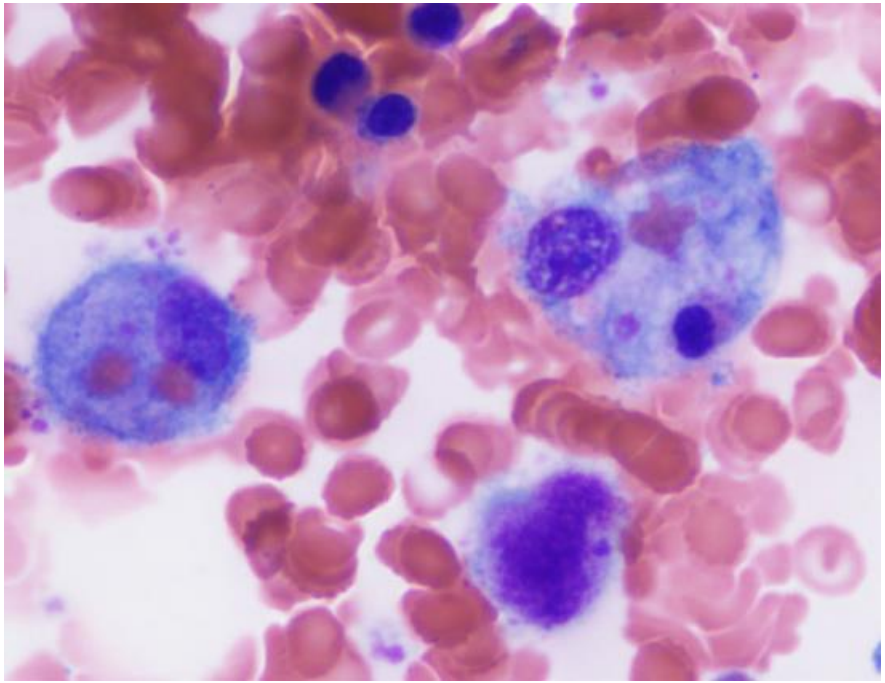
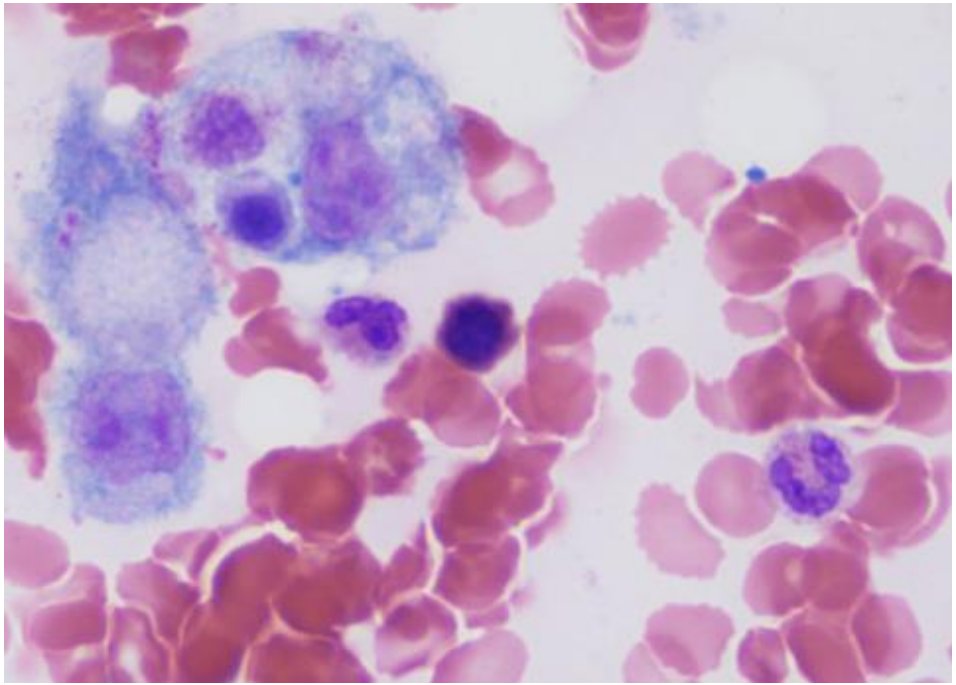
Hemophagocytic histiocytes





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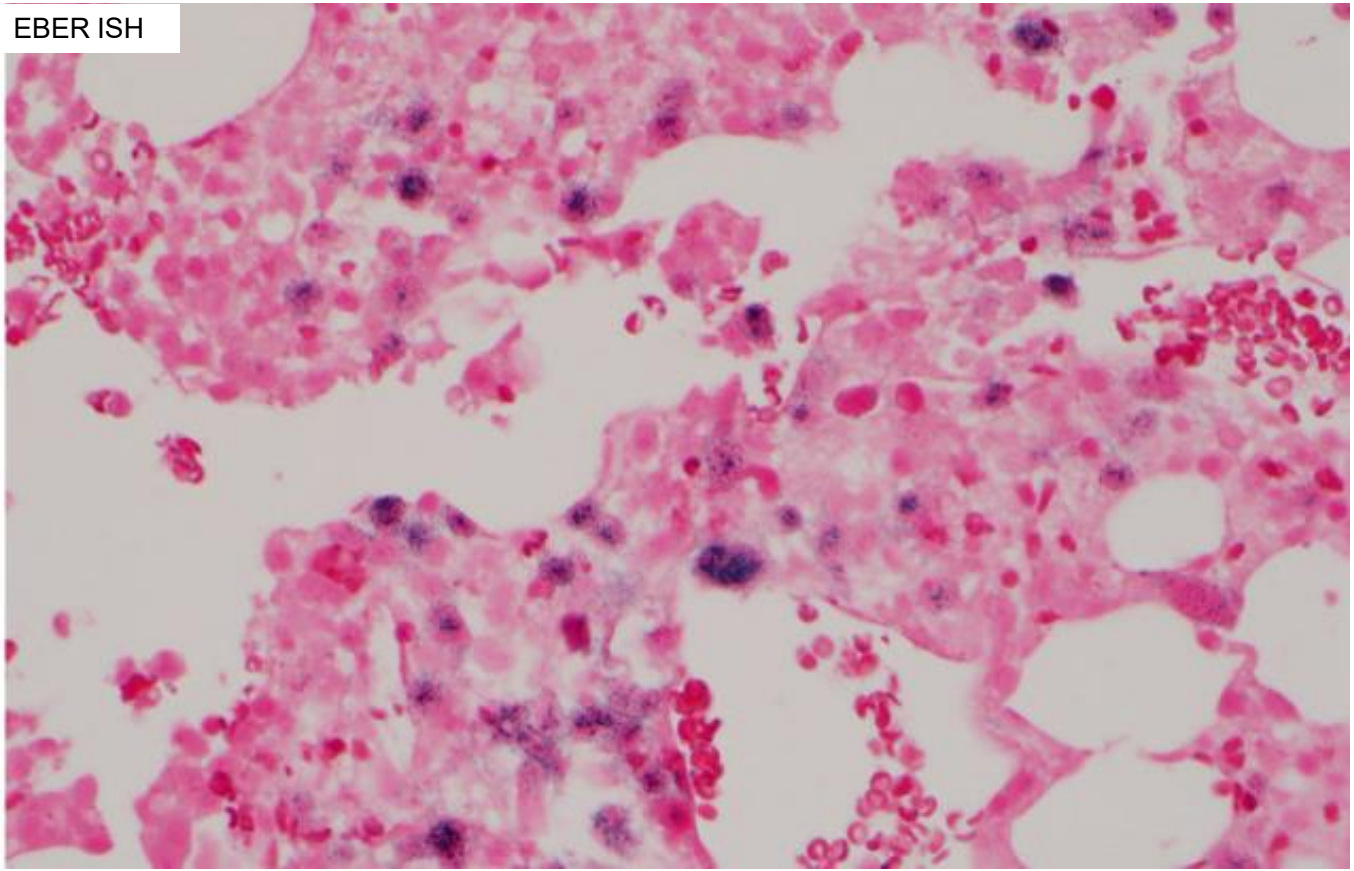
EBER ISH



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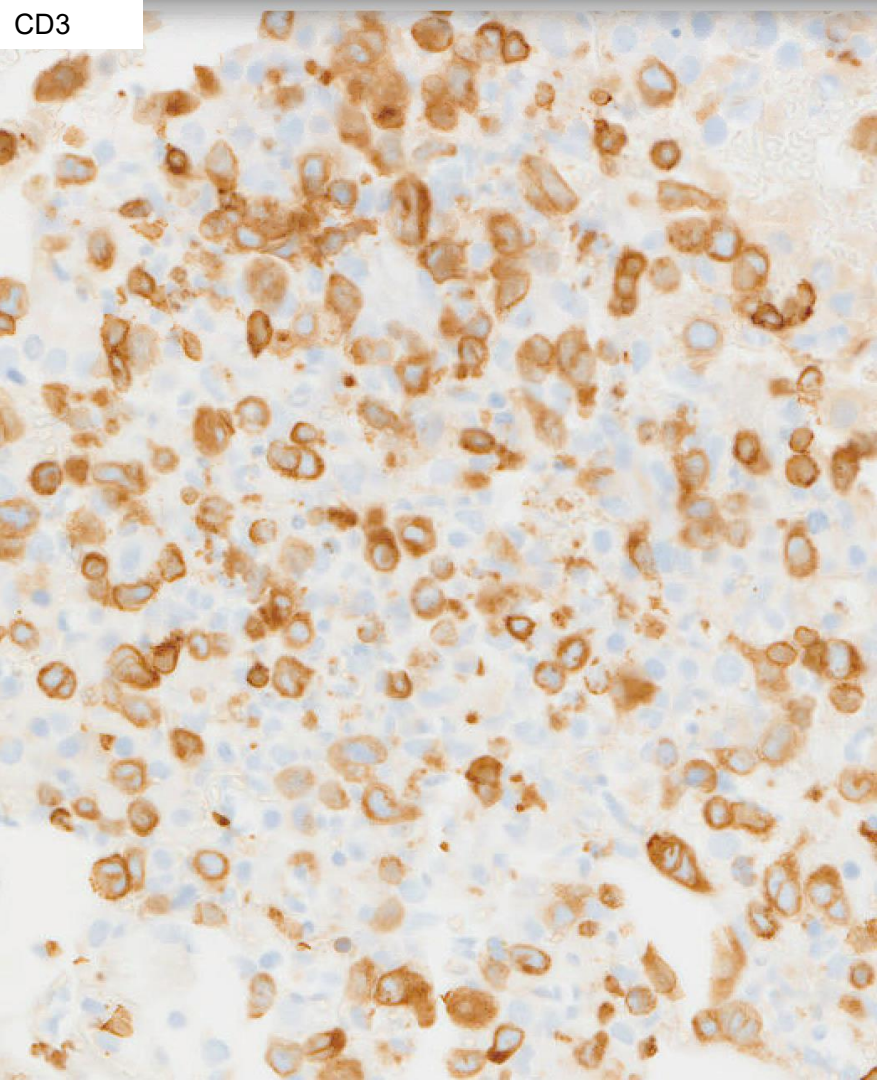
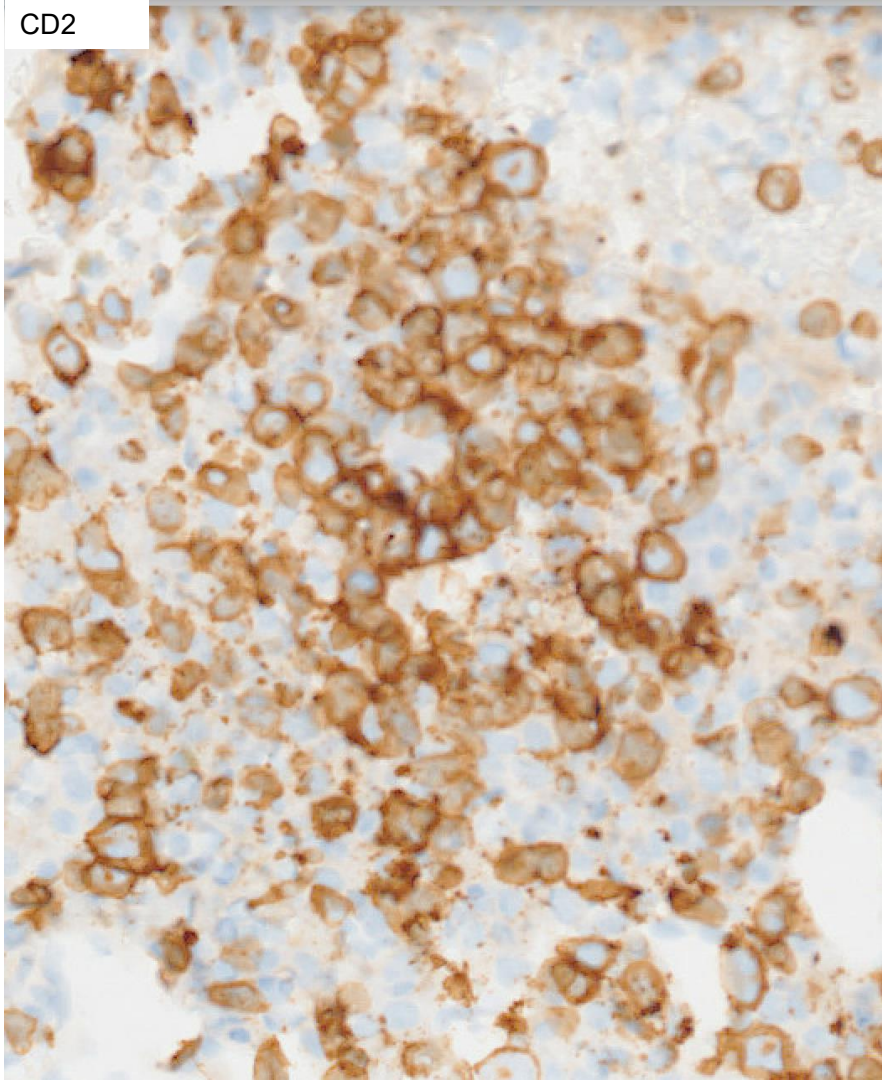
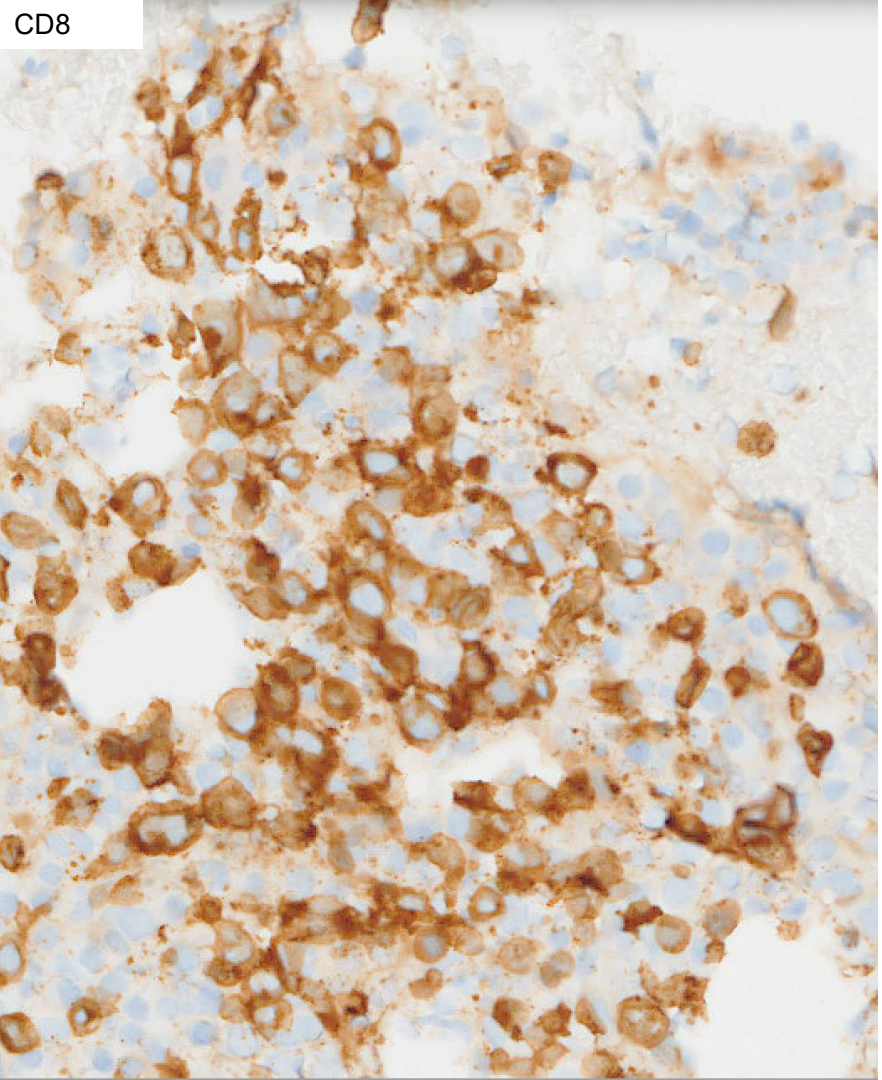
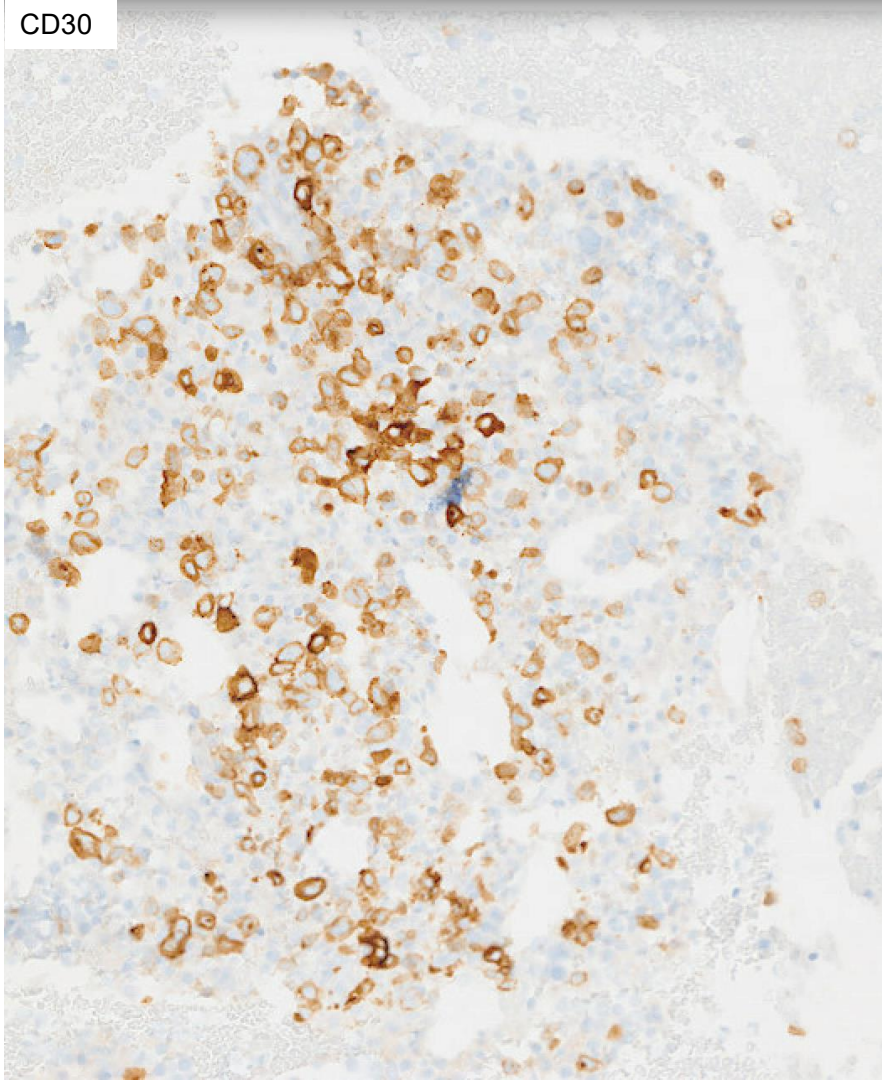

CD3


CD2

CD8



CD30



Immunophenotype Recap:

Positive: CD45, CD3, CD2, **CD8**, MUM-1, **CD30**, **EBER-ISH,**

Negative: **CD56**, CD4, CD5, CD15, ALK-1, HHV-8 or Granzyme B

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T Cell Receptor Gene Rearrangement:

- Positive for t-cell receptor gamma chain monoclonal gene rearrangement

FISH:

Negative for rearrangements of ALK, BCL6, MYC, IGH, MYC-IGH, CCND1-IGH, BIRC3-MALT1, and IGH-BCL2 genes.
However, the interphase FISH signal pattern was consistent with loss of BIRC3 (11q21) and MALT1 (18q21) in 14.5% and also a loss of BCL2 (18q21) in 13.5% of the nuclei analyzed.
Concurrent cytogenetic analysis also showed a complex karyotype with loss of multiple chromosomal regions involving 6q, 11q, 18, 17p etc.

Differential Diagnosis

- Aggressive NK-cell leukaemia
- Primary nodal EBV-positive T- and NK-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Systemic EBV-positive T-cell lymphoma of childhood
- EBV -associated haemophagocytic lymphohistiocytosis
- Chronic active EBV disease, systemic form (T- or NK-cell type)

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- Aggressive NK-cell leukemia
  - Clonal CD56(+) NK-cell malignancy; with surface CD3 (-) and cytoplasmic CD3ε (+)

- Primary nodal EBV-positive T- and NK-cell lymphoma
  - Confined to the lymph nodes (mass forming), can be NK phenotype (CD56+), aggressive but not fulminant

- Extranodal NK/T-cell lymphoma, nasal type
  - NK-cell origin ($CD56^+$), mass-forming lesion that is localized to the nasal/upper aerodigestive tract
  - Usually shows angiocentric necrosis

- Systemic EBV-positive T-cell lymphoma of childhood
  - Clonal $CD8^+$ cytotoxic T cells (CD3+), EBER (+), CD56(-)
  - Systemic disease: bone marrow, lungs
  - Clinical: Fulminant, rapidly fatal course with HLH features.

- EBV -associated haemophagocytic lymphohistiocytosis
  - Reactive, polyclonal activation of cytotoxic T/NK cells
  - No clonal T-cell proliferation or marked atypia

- Chronic active EBV disease, systemic form (T- or NK-cell type)
  - Mostly polyclonal, indolent with persistent EBV infection
  - Reactive appearing lymphocytes (not atypical)

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Differential Diagnosis

Entity	Typical age	TCR clonality	Key features
EBV-HLH	Pediatric	Polyclonal	Reactive, self-limited
CAEBV	Child/adult	Oligoclonal	Chronic, organ infiltration
SEBVTCL	Child/adult	Monoclonal	Fulminant, HLH, fatal
ENKTCL	Adult	NK-cell, cytotoxic	Extranodal, MYC-high

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Diagnosis

Systemic EBV+ T Cell Lymphoma "of Childhood"
Associated with Hemophagocytic Lymphohistiocytosis

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Discussion:

Comprehensive genomic datasets studying SEBVTCL remain limited.

Some studies looking into gene expression profiling in Epstein–Barr virus (EBV)-associated T/natural killer (NK)-cell lymphoproliferative disorders in children and young adults:

- Chronic active Epstein–Barr virus (EBV) infection of T/natural killer (NK)-cell type (CAEBV-T/NK)
- Systemic EBV-positive T-cell lymphoma of childhood

Revealed that these entities have similar molecular and phenotypic signatures to nasal-type NK/T-cell lymphoma (NKTL), with overexpression of p53, survivin and EZH2.

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Ng et al, *Leukemia & Lymphoma* 2015

NYU Myeloseqer NGS - Molecular Pathology

Gene	Variant	Tier	Variant Type	VAF(%)	Depth	Transcript
TP53	c.517G>A, p.V173M	2	SNV	6.10	2000	NM_000546.6
BCOR	c.2752C>T, p.Q918Ter	2	SNV	7.50	1999	NM_001123385.2

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Discussion:

EBV-driven T/NK-cell lymphomas frequently carry driver lesions in TP53 and BCOR.

TP53 disruption is consistently associated with adverse outcomes in EBV-positive T/NK neoplasms

BCOR (a PRC1.1 corepressor) mutations are recurrent and linked to MYC dysregulation and poor risk in ENKTCL cohorts.

In the context of a fulminant EBV-positive cytotoxic T-cell neoplasm presenting with HLH, these mutations support a high-risk biology and strengthen the rationale for prompt HLH control, followed by curative-intent allogeneic transplantation once feasible

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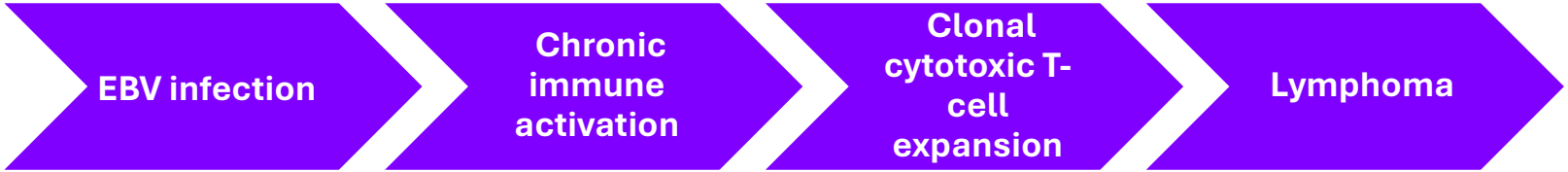
Oishi et al., *Blood Adv*, 2022
Johnson et al., *Blood Adv*, 2023

Discussion-Pathogenesis



- EBV latent genes (LMP1, EBNA1) activate NF-κB and JAK/STAT pathways.
- TP53 loss disables apoptosis and antiviral checkpoints.
- BCOR loss disrupts PRC1.1 leading to MYC upregulation and epigenetic reprogramming.
- Result: Uncontrolled cytotoxic proliferation, cytokine storm → **HLH**.

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Prognostic Summary of SEBVTCL

- Aggressive, often fatal without transplant.
- Median survival <6 months in historical series.
- BCOR/TP53 alterations confer additional adverse risk.
- Successful outcomes primarily with rapid HLH control and early HSCT.

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Hospital Course

Patient could not be treated for her T- Cell lymphoma due to multi organ failure and ultimately passed away after a 20 day hospital course

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References

- Ng, Siok-Bian, et al. “Epstein–Barr Virus-Associated T/Natural Killer-Cell Lymphoproliferative Disorder in Children and Young Adults Has Similar Molecular Signature to Extranodal Nasal Natural Killer/T-Cell Lymphoma but Shows Distinctive Stem Cell-like Phenotype.” *Leukemia & Lymphoma*, vol. 56, no. 8, Aug. 2015, pp. 2408–15.
- Oishi N, et al Genetic and immunohistochemical profiling of NK/T-cell lymphomas reveals prognostically relevant BCOR-MYC association. Blood Adv. 2023 Jan 10;7(1):178-189. PMID: 35882439; PMCID: PMC9837655.
- Johnson WT, et al TP53 mutations identify high-risk events for peripheral T-cell lymphoma treated with CHOP-based chemotherapy. Blood Adv. 2023 Sep 12;7(17):5172-5186.PMID: 37078708; PMCID: PMC10480533.
- Tse, E., Zhao, WL., Xiong, J. et al. How we treat NK/T-cell lymphomas. J Hematol Oncol 15, 74 (2022).
- Montes-Mojarro, Ivonne A. et al. Mutational profile and EBV strains of extranodal NK/T-cell lymphoma, nasal type in Latin America, Modern Pathology, Volume 33, Issue 5, 781 - 791

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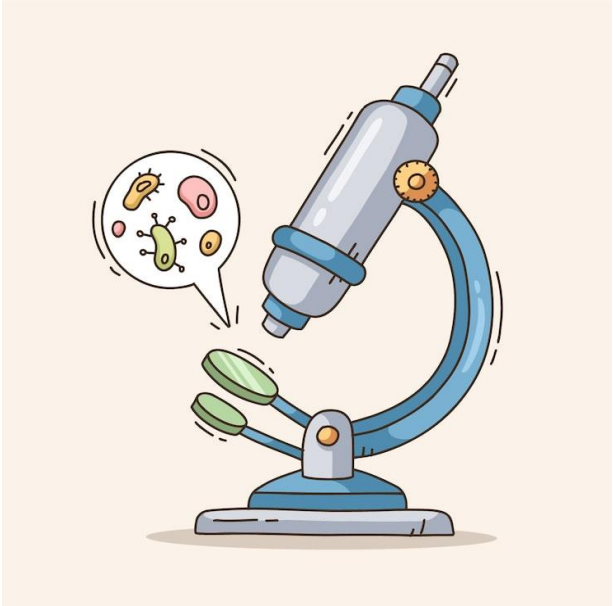
Acknowledgments

NYU Hematopathology:

- **Dr. Abdallah Flaifel – Reviewing case & developing presentation**
- **Dr. Nicholas Ward – Diagnosis & review of case**

NIH Hematopathology



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