Concurrent Hemophagocytosis and Hodgkin Lymphoma-Type Richter Transformation in CLL/SLL: An Incidental Finding with Therapeutic Implications

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INTRODUCTION

- **Richter transformation (RT)** to classic Hodgkin lymphoma (CHL) accounts for ~10% of RT cases in CLL/SLL
- **Hemophagocytic lymphohistiocytosis (HLH)** complicating CLL/SLL is exceedingly rare
- We report a case of **incidental hemophagocytosis discovered during bone marrow workup for suspected RT in CLL/SLL**, subsequently confirmed by specialized HLH biomarkers.

DISCUSSION

- **Atypical CD15−/EBER− phenotype** raises the question of true CHL-type RT versus CLL with Hodgkin/Reed-Sternberg-like cells
  - Significant prognostic implications (median OS 57 vs. 8.4 months with Hodgkin-directed therapy vs CLL-directed therapy in CLL-HRS).
- **Radiographic-clinical paradox**
  - Mediastinal nodes regressed on serial CT
- **Bone marrow rescued the diagnosis** after a non-diagnostic node biopsy
- **Diagnostic masking by the underlying malignancy**
  - B symptoms and pancytopenia initially attributed to CLL/SLL progression and suspected RT
- **HLH features overlap**
  - Easily obscured by the underlying lymphoproliferative disorder
- **Hemophagocytosis alone is not HLH:**
  - **Specialized biomarkers** (sCD25/sIL-2Rα, CXCL9, IL-18) provided the confirmatory evidence

CONCLUSIONS

- **This case highlights three key points:**

(1) The importance of pursuing tissue diagnosis despite improving imaging when clinical suspicion for RT is high

(2) The diagnostic value of bone marrow biopsy when lymph node sampling is nondiagnostic

(3)The role of specialized biomarkers in confirming HLH

CASE PRESENTATION

Patient history:

- **85-year-old female with CLL/SLL** (Rai Stage IV, Binet Stage C, IGHV unmutated, FISH: trisomy 12), previously treated with Acalabrutinib, currently on Venetoclax + Obinituzumab
- **Presented with B-symptoms** (fever, night sweats, unintentional weight loss) and **pancytopenia** (WBC 2.10 K/μL, ANC 1200/μL, hemoglobin 10.6 g/dL, platelets 76 K/μL)
- **Neutropenic fever** treated with cefepime for 7 days
- **Hypogammaglobulinemia** (IgG 317 mg/dL) treated with IVIG 400 mg/kg
- **Radiographic improvement of mediastinal nodes** on imaging, noted mild splenomegaly

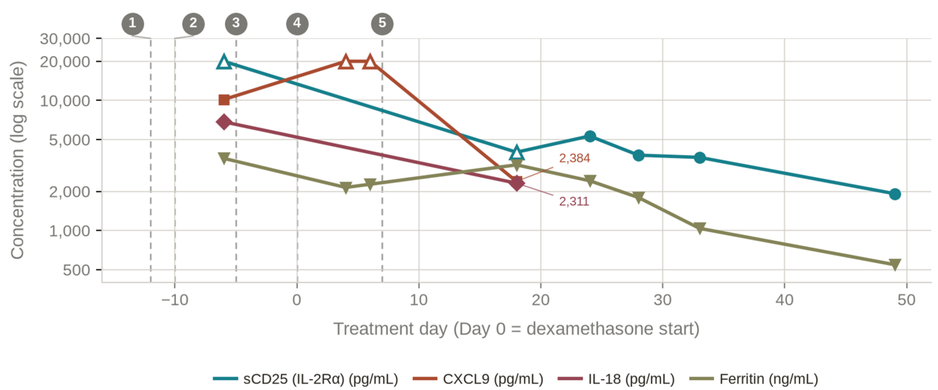
Nodal Site	Prior	Current
Subcarinal	7 x 4 cm	4.8 x 1.4 cm
Paratracheal	4.6 x 3.7 cm	1.9 x 1.2 cm

Table 1. Nodal size comparison of previous and current imaging

Lymph Node Biopsy	• Non-diagnostic tissue fragments • Equivocal EBER-ISH • Lesional cells lost on deeper sections — PAX5/CD30 confirmation precluded
Bone Marrow Biopsy	• Hypercellular, increased histiocytes with clustering • Scattered large atypical cells: CD20−, PAX5+, CD30+, CD15−, EBER-ISH− • No residual CLL identified

Inflammatory Biomarker Response to HLH-Directed Therapy

Log-scale trend by treatment day, with key clinical events annotated



CLINICAL EVENTS

1 Initial marrow biopsy — Day −12
2 Neutropenic fever / cefepime — Day −10
3 IVIG — Day −5
4 Dexamethasone start — Day 0
5 Etoposide added — Day 7

▵ = value above the assay's quantifiable ceiling (true value higher). IL-18 measured at two timepoints only.

Biomarker	Day 0	Most recent available	Reference range
CXCL9, pg/mL	10,159	2,384 (Day 18)	≤647
IL-18, pg/mL	6,847	2,311 (Day 18)	≤468
sCD25 (IL-2Rα), pg/mL	≥20,000	1,919 (Day 49)	622–1,619
Ferritin, ng/mL	3,587	546 (Day 49)	20–175

Marker	Lymph node Bx	Marrow Bx
CD20	Not assessable*	Negative
PAX5	Not assessable*	Positive
CD30	Not assessable*	Positive
CD15	Not performed	Negative
EBER-ISH	Equivocal	Negative
Residual CLL	N/A	None identified

Table 2. Immunohistochemical Comparison of Lymph Node and Bone Marrow Biopsy Findings; *lesional cells lost on deeper sections

- **HScore** = 187 points, corresponding to ~70-80% probability of HLH
- **OHI index positive**: the optimized HLH inflammatory index (sCD25 >3,900 U/mL and ferritin >1,000 ng/mL)
- Treated with **dexamethasone (Day 0)** per HLH-94 protocol with transient decrease in inflammatory markers
- **Etoposide** eventually initiated **(Day 7)** after increasing inflammatory markers

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