A Snapshot in Time: The Challenge to Meet Diagnostic Criteria in a Patient with Hemophagocytic Lymphohistiocytosis

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Objectives

1. Define and challenge diagnostic criteria in rare conditions.
2. Recognize that malignancy can be an underlying cause of hemophagocytic lymphohistiocytosis (HLH), even in an adult with rheumatologic disease, and that treatment varies with etiology.

Case Information

- 72-year-old woman with well-controlled rheumatoid arthritis with 4 months of fevers, night sweats, and malaise

Presented to outside hospital

- Work-up revealed hepatosplenomegaly, pancytopenia, and liver injury
- Unrevealing bone marrow and liver biopsies. No tx given

Transferred to tertiary care center due to ongoing concern for HLH/MAS

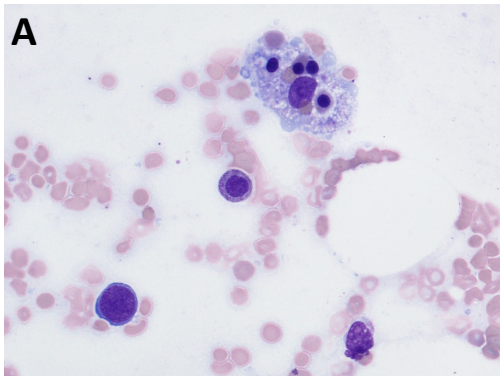
- Admission labs notable for:
  - Pancytopenia (WBC 1.2 x 10^9/L, ANC 1 x 10^9/L, Hgb 8 g/dL, Plt 25 x 10^9/L)
  - Elevated ferritin (7905 ng/mL)
  - Liver injury (ALT 79 U/L, AST 105 U/L, ALP 745 U/L, Tbili 5 mg/dL, INR 1.6)
  - Elevated triglycerides (147 -> 303 mg/dL on HD 6)
  - Decreased fibrinogen (1.54 -> 0.78 g/L on HD 3)
- Now met diagnostic criteria for HLH

Hospital course at tertiary care center

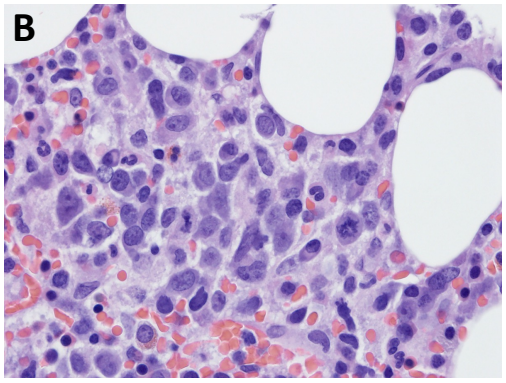
- Started on steroids alone for known RA due to no finding of underlying malignancy
- Outside pathology upon re-review showed hemophagocytosis
- Elevated soluble IL-2 receptor (78,453 pg/mL) and CXCL9 (30,238 pg/mL)
- No improvement on steroids alone, so anakinra, then etoposide were initiated
- Disease progressed; patient transitioned to comfort-care
- Underlying HLH etiology was eventually confirmed on repeat bone marrow biopsy to be T-cell lymphoma

Discussion

- HLH is a hyper-inflammatory disease that arises from genetic immune system defects or, in adults, is more commonly triggered as a complication of malignancy, infection, or rheumatologic disease.
- Diagnosis is defined by meeting a set of criteria that were designed for research purposes.
- **The dilemma**: **early treatment is essential** BUT 3 HLH diagnostic criteria have **long send-out times** and a 4th requires biopsy.
- By the time our patient met criteria, her status had already deteriorated.
- **Evaluation represents A SNAPSHOT IN TIME. Conditions change**
- Diagnosis initially missed by "gold-standard" pathology.
- Treatment was also delayed by initial suspicion due to her history of RA for macrophage activation syndrome (MAS), which is treated with anakinra rather than etoposide.



A. A histocyte from an aspirate smear contains multiple erythroid precursors and mature red blood cells and shows rounded nuclear contours with cytoplasmic projections. The findings are compatible with hemophagocytic lymphohistiocytosis (HLH).



B. The bone marrow biopsy shows an atypical lymphocytic infiltrate comprised of medium to large lymphocytes with pleomorphic, irregular nuclei and prominent nucleoli. Flow cytometric analysis of the atypical lymphocytes shows that they are positive for CD45, surface and cytoplasmic CD3, CD8, CD2, CD7, TCR-alpha/beta, TIA-1, CD38, and CD30. Immunohistochemical stains showed the atypical lymphocytes were positive for CD3, CD2, CD7, CD30, TIA-1, TCR-beta F1, Perforin, Granzyme B, and CD8. The findings are consistent with peripheral T-cell lymphoma, not otherwise specified (NOS), with cytotoxic phenotype and variable CD30 expression.

Revised Diagnostic Guidelines for HLH from Henter et. al. (2007)[1]

The diagnosis of HLH can be established if either 1 or 2 below is fulfilled.

(1) A molecular diagnosis consistent with HLH

(2) Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below)

A. Initial diagnostic criteria
- Fever
- Splenomegaly
- Cytopenias (≥ 2 of 3 lineages)
  - Hemoglobin <90 g/L
  - Platelets <100 x 10^9/L
  - Neutrophils <1.0 x 10^9/L
- Hypertriglyceridemia and/or hypofibrinogenemia
  - Fasting triglycerides ≥ 3.0 mmol/L (265 mg/dL)
  - Fibrinogen ≤ 1.5 g/L
- Hemophagocytosis in bone marrow or spleen
- No evidence of malignancy

B. New diagnostic criteria
- Low or absent NK-cell activity
- Ferritin ≥ 500 microgram/L
- Soluble CD25 (i.e. soluble IL-2 receptor) ≥ 2400 U/mL

Key Takeaways

This case exemplifies:

1. The challenge of reliance on diagnostic criteria before initiating treatment
2. The difficulty of relying on subjective results as a "gold-standard"
3. The importance of determining the underlying cause to guide therapy

References

1. Henter J, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-131. doi:10.1002/PBC.21039