Beyond the Criteria:

Diagnosing Hemophagocytic Lymphohistiocytosis With Multiple Competing Inflammatory and Malignant Processes

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UCONN HEALTH

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome associated with profound immune dysregulation.

Overlapping inflammatory and malignant processes can complicate HLH diagnosis, as each may independently explain individual clinical findings while also contributing to the underlying hyperinflammatory state.

PATIENT AND PRESENTATION

82-year-old man with chronic lymphocytic leukemia (CLL), steroid-refractory warm autoimmune hemolytic anemia (wAIHA), and metastatic melanoma previously treated with nivolumab presented with intermittent melena and diarrhea.

Although constitutional symptoms were absent at presentation, his hospital course was marked by persistent fevers, lymphadenopathy, and progressive splenomegaly despite broad-spectrum antibiotic therapy and an extensive negative infectious evaluation.

CLINICAL DETERIORATION

His course rapidly progressed to encephalopathy, severe neutropenia, coagulopathy, and distributive shock with multiorgan failure requiring prompt ICU admission.

The combination of persistent inflammation and accelerating organ dysfunction prompted reassessment for HLH, although given his considerable clinical decline, there was limited opportunity for histopathological diagnosis.

EVIDENCE SUPPORTING HLH

>33,500 ng/mL

FERRITIN

77,516 U/mL

SOLUBLE INTERLEUKIN-2 RECEPTOR

Hypofibrinogenemia
Progressive cytopenias
Undetectable haptoglobin

6 of 8 HLH-2004 criteria met

Reported HScore-derived probability: 99%

DIAGNOSTIC INTERPRETATION

Competing process	Overlapping findings
CLL	Cytopenias, lymphadenopathy, splenomegaly
Warm AIHA	Anemia and undetectable haptoglobin
DIC / coagulopathy	Hypofibrinogenemia and cytopenias
Possible infection	Fever, shock, and organ dysfunction

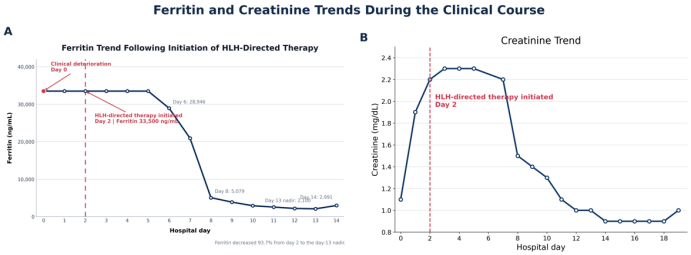
DISCUSSION

Individual findings each had plausible competing explanations: cytopenias could reflect CLL or autoimmune hemolysis, while fevers, lymphadenopathy, and splenomegaly could be attributed to infection or malignancy.

An unrevealing infectious evaluation and continued clinical deterioration despite broad-spectrum antibiotics weakened support for infection as the sole explanation.

The co-occurrence of clinical findings with marked hyperferritinemia, hypofibrinogenemia, and rapidly progressive multiorgan dysfunction raised concern for a unifying hyperinflammatory syndrome.

TREATMENT AND RESPONSE



Given progressive decline, the team initiated HLH-directed therapy prior to histologic confirmation. While the treatment response supported the clinical diagnosis, the relative contribution of each co-occurring clinical process remained uncertain.

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KEY LEARNING POINT

The Diagnostician must interpret HLH criteria within the evolving clinical context. In this patient, converging clinical evidence and rapid clinical deterioration prompted initiation of treatment *before* histologic confirmation.