Case Report

Hemophagocytic Lymphohistiocytosis (HLH) Associated with T-Cell Lymphomas: Broadening our Differential for Fever of Unknown Origin

Sherrie Khadanga, Benjamin Solomon, Kim Dittus[1]

Department of Medicine, [1]Division of Hematology/Oncology, University of Vermont, Vermont, United States

Abstract

Context: Hemophagocytic lymphohistiocytosis (HLH), due to the excessive activity of histiocytes and lymphocytes, is a rare but aggressive disease that typically occurs in infancy but can be seen in all ages. If left untreated, patients with HLH may live for only a few months and die from multi-organ failure. **Case Report:** We present two cases of HLH diagnosis. Fever, spleen, and hepatic abnormalities were noted in both cases. **Conclusion:** Early diagnosis is the key and these two cases of similar etiology highlight how fever of unknown origin should force us to broaden our differential.

Keywords: Fever of unknown origin, Hemophagocytic lymphohistiocytosis, T-cell lymphoma

Address for correspondence: Dr. Sherrie Khadanga, Department of Medicine, University of Vermont, 111 Colchester Avenue, Fletcher 311, Burlington, Vermont-05401, USA. E-mail: sherrie.khadanga@vtmednet.org

Introduction

Affecting 1.2 people per million, Hemophagocytic lymphohistiocytosis (HLH) is an autoimmune dysregulatory syndrome resulting in severe inflammation and multi-organ failure. HLH is rare in adults and may have various triggering etiologies. Diagnosis is made if five of eight criteria are fulfilled: Fever, splenomegaly, cytopenia, hyperlipidemia (and/or hypofibrinogenemia), hemophagocytosis, low/absent NK-cells, ferritin >500 microg/L, and soluble CD25/IL-2 receptor ≥2,400 U/ml.[1] We present two cases of HLH diagnosis [Table 1].

Case Presentation

Case 1

A 78-year-old female presented with fatigue, hypercalcemia, and weight loss, which she attributed to an infection. Her symptoms progressed to high-grade fever with persistent lethargy and worsening pancytopenia. CT revealed lung and liver nodules and splenomegaly with lesions. Liver biopsy initially revealed vague granulomatous features with spindle histiocytoid and epitheliod infiltrates. Similar features were noted in bone marrow aspirate [Figure 1]. The patient deteriorated clinically while waiting for a definitive diagnosis. Presumed diagnosis of HLH was made. She received steroids according to the HLH94 protocol but was too ill to receive etoposide, and she subsequently passed away. Autopsy and final liver biopsy confirmed HLH with T-cell NHL. Images of spleen and liver with corresponding microscopics [Figure 1] showed scattered large atypical cells (CD30+ with aberrant T-cell phenotype) in a background of small lymphocytes.

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.141656

Case 2

A 69-year-old male presented with nightly fevers for 6 weeks, hepatosplenomegaly, and pancytopenia. Bone marrow biopsy showed non-caseating granulomas and CD163+ staining. CT A/P revealed splenic and hepatic lesions and splenomegaly [Figure 2]. A liver biopsy was consistent with HLH and he was started on HLH94 protocol. Eventually, his liver biopsy revealed

Table 1: Overview of hemophagocytic lymphohistiocytosis (HLH) diagnostic criteria

Criteria	Case 1 78-year-old female	Case 2 69-year-old male
Fever	Yes	Yes
Splenomegaly	Yes	Yes
Cytopenia (affecting ≥2 of 3 lineages)	Yes	No
Hypertriglyceridemia and/ or Hypofibrinogenemia	Yes	Yes
Hemophagocystosis in bone marrow, spleen or lymph nodes	Yes	Yes
Low or absent NK-cell* activity	No	No
Ferritin ≥500 microg/L	Yes	Yes
Soluble CD25/IL-2 receptor ≥2,400 U/mL	Not Tested	Yes

*NK-cell = Natural killer cell

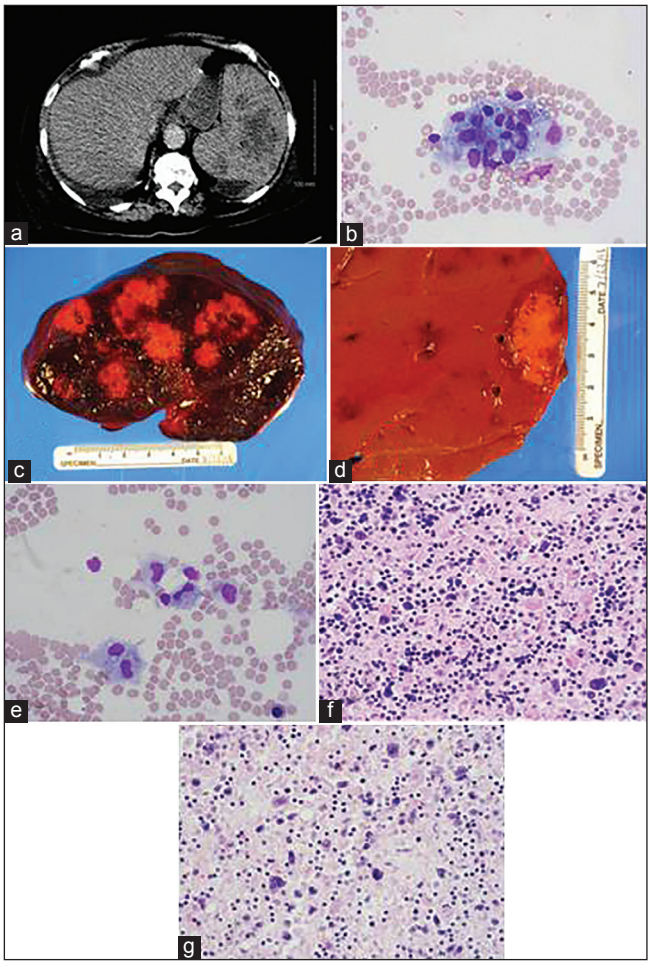

Figure 1: (a) CT showing lung and liver nodules and splenomegaly with lesions. (b and c) Bone marrow aspirate revealing vague granulomatous features with spindle histiocytoid and epitheliod infiltrates. (d and e) Images of spleen and (f and g) images of liver, all with corresponding microscopics showing scattered large atypical cells (CD30+ with aberrant T-cell phenotype) in a background of small lymphocytes

hepatosplenic T-cell lymphoma with associated HLH. He was then started on ICE chemotherapy and after finishing cycle 1 therapy is currently on s/p cycle 2. A donor search is ongoing.

Discussion

The interval between diagnosis and treatment for HLH is quite variable and decreasing the time to begin initial treatment is critical. Immunosuppressant agents can prevent progression to multi-organ failure, the most common cause of death in HLH.[2] HLH deserves consideration in a work-up for patients with Systemic Inflammatory Response Syndrome (SIRS) of unknown etiology, especially with unexplained cytopenia, hepatosplenomegaly, and fevers.[3] Definitive diagnosis is often difficult as the hallmark clinical feature, histiologic demonstration of hemophagocytosis, is neither sensitive nor specific.[4] Timely diagnosis requires early clinical suspicion to institute testing and treatment. The only available HLH treatment guidelines HLH-1994 and HLH-2004 are based on studies involving pediatric populations, which include a mixture of both primary and secondary HLH.[5] An alternative diagnostic approach proposed broader modalities defining HLH by its pathophysiology including tests of immunodeficiency, immune activation, and abnormal immunopathology.[6]

HLH in adults remains a disorder about which a lot remains to be known; treatments include immunosuppressive and immunomodulating agents, cytostatic drugs, and certain biologic response modifiers.[3] Prognosis in adult populations is poor with overall mortality of 67% in one retrospective study.[5] Current treatment standards are still widely based on the original HLH-1994 guidelines. In adults, HLH is nearly always secondary to a trigger,

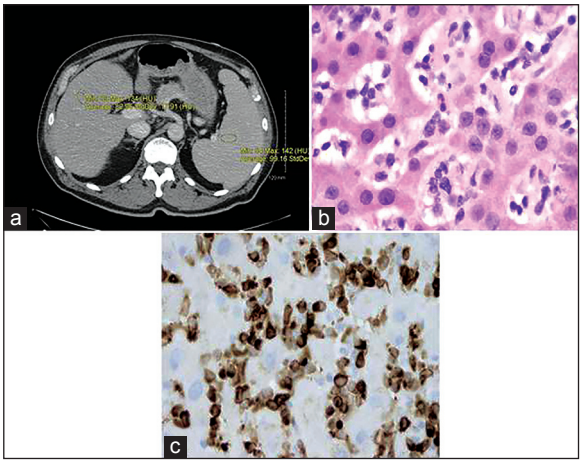

Figure 2: (a) CT of Abdomen/Pelvis showing splenic and hepatic lesions and splenomegaly. (b) Liver biopsy revealing non-caseating granulomas. (c) CD3 antibody staining, indicating T-cell activation

and identification and treatment of the primary etiology is essential for a possible cure. Early diagnosis remains the key, and these two cases of similar etiology should force us to broaden our differential. Even though rare and sometimes unique in its presentation in adult populations, further research is needed for this fatal disease.

Acknowledgment

The authors express their gratitude to Gurpreet Lamba, M.D., Assistant Professor, Division of Hematology/Oncology, University of Vermont, for emphasizing the importance of "fever of unknown origin" and its diagnostic value. His assistance in image processing is also appreciated.

References

1. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: An update on diagnosis and pathogenesis. Am J Clin Pathol 2013;139:713-27.
2. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
3. Kleynberg RL, Schiller GJ. Secondary hemophagocytic lymphohistiocytosis in adults: An update on diagnosis and therapy. Clin Adv Hematol Oncol 2012;10:726-32.
4. Gupta A, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemopgaocytic lymphohistiocytosis. Pediatr Blood Cancer 2008;50:192-4.
5. Shabbir M, Lucas J, Lazarchick J, Shirai K. Secondary hemophagocytic syndrome in adult series of 18 patients in a single institution and a review of literature. Hematol Oncol 2010;29:100-6.
6. Jordan MD, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041-52.

How to cite this article: Khadanga S, Solomon B, Dittus K. Hemophagocytic lymphohistiocytosis (HLH) associated with T-cell lymphomas: broadening our differential for fever of unknown origin. North Am J Med Sci 2014;6:484-6.

Source of Support: Nil. **Conflict of Interest:** None declared.