A Slow Burning Diagnosis: A Case Report of Hemophagocytic Lymphohistiocytosis Preceding the Diagnosis of Subcutaneous Panniculitis-Like T-Cell Lymphoma

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INTRODUCTION

HLH is a severe inflammatory syndrome characterized by primary or secondary immune dysregulation causing excess activation of macrophages and cytotoxic lymphocytes, leading to multi-system dysfunction. Diagnosing and managing HLH can be challenging for clinicians, with HLH-2004 criteria for diagnosis requiring a molecular diagnosis or the presence of at least five of the following: fever, splenomegaly, cytopenia involving two or more cell lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen or lymph nodes with no evidence of malignancy, low or no NK cell activity, elevated ferritin, or elevated soluble IL-2 receptor[1]. These criteria have been utilized to develop the HScore, a tool used to assist in determining the probability of HLH based on the aforementioned abnormalities[2]. After diagnosis, treatment typically includes chemotherapy and immunosuppression, followed by allogeneic bone marrow transplant[3].

CASE PRESENTATION

A 27-year-old Vietnamese female with no past medical or family history presented to the emergency department with three weeks of intermittent fevers, headache, and unilateral neck swelling. She immigrated to the United States from Vietnam five years prior. She denied any recent travel, environmental exposures, sick contacts, or chronic medications. She denied shortness of breath, cough, nausea, vomiting, or diarrhea.

On examination, temperature was 39.2°C, heart rate 110 beats per minute, blood pressure 112/74 mmHg, respiratory rate 16 breaths per minute, and oxygen saturation 96% on room air. Scleral icterus was absent. She was tachycardic with regular cardiac rhythm, and lungs were clear to auscultation bilaterally. Two mobile, non-tender, left-sided cervical lymph nodes measuring 1-2cm each were palpated without further lymphadenopathy. Her abdomen was non-tender, non-distended, and normoactive. Her skin was dry, without rashes, petechiae, or ecchymoses.

Initial laboratory workup was notable for a hemoglobin of 8.4 g/dL, white blood cell count of 2.9 B/L with normal differential, aspartate aminotransferase (AST) of 308 IU/L, and alanine aminotransferase (ALT) of 248 IU/L. Chest radiography was negative for any acute process. Computed tomography of the neck, chest, abdomen, and pelvis noted trace pleural effusions, abdominopelvic ascites, hepatosplenomegaly, and diffuse colitis. Blood and urine cultures (including acid fast and fungal cultures) showed no growth.

A comprehensive infectious, hematologic, and rheumatologic workup was performed, including mycobacterial, fungal, malarial, and zoonotic testing; invasive studies included lumbar puncture, paracentesis, cervical excisional lymph node biopsy, liver biopsy, and laparoscopy with mesenteric and lymph node biopsy. There was no evidence of active acute infection, malignancy, or autoimmune disease on serologic testing. Liver biopsy showed chronic hepatitis with minimal-mild activity and no fibrosis. Peritoneal fluid showed reactive mesothelial cells without evidence of malignancy, and fluid cultures were negative. Mesenteric and lymph node biopsy showed benign lymph nodes with reactive sinus histiocytosis and focal necrosis; acid fast and fungal stains were negative. Bone marrow biopsy and peripheral flow cytometry revealed a hypercellular bone marrow with trilineage hematopoiesis, occasional hemophagocytosis, adequate iron, and no evidence of leukemia/lymphoma. Findings were discussed with hematopathology and medical oncology services, and ultimately felt to be inconclusive. She was discharged home with ongoing fevers but clinically stable, with plans for outpatient follow-up.

Four months after discharge, she presented again with nausea, vomiting, and fever. She reported returning to Vietnam and being hospitalized there with similar but worsening symptoms. A diagnostic workup from that hospitalization, including bone marrow biopsy, was unrevealing. She reported generalized myalgias, epistaxis, malaise, and abdominal pain. On exam, temperature was 40.6°C, heart rate 105 beats per minute, blood pressure 90/64 mmHg, respiratory rate of 25 breaths per minute,

and oxygen saturation 95% on room air. Physical exam noted scleral icterus. She had sinus tachycardia, and lungs were clear to auscultation bilaterally. Her abdomen was diffusely tender to palpation with guarding, and her liver edge was palpable. Ecchymoses were present diffusely, and crusted blood was visualized in the nares. Labs were notable for Hgb 8.6 g/dL, WBC 6.8 B/L with 86% neutrophils, platelets 35 B/L, AST 3200 IU/L, AST 680 IU/L, triglycerides 273 mg/dL, ferritin 75910 ng/dL, fibrinogen 40 mg/dL, and IL-2R of 30470 pg/mL; total HScore was 299. After receiving steroids, intravenous fluids, and broad-spectrum antibiotics, she was admitted to the medical intensive care unit and initiated on dexamethasone and etoposide per the HLH-94 protocol with improvement in her clinical condition. She was discharged home two weeks later, successfully completing a taper of dexamethasone and weekly etoposide infusions with her oncologist.

Approximately eight months after discharge, she was seen by Dermatology for erythematous firm plaques with ulceration on her thigh that persisted for several months despite oral antibiotics. She underwent punch biopsy of the lesion twice; her first biopsy was inconclusive, and second biopsy demonstrated subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with immunohistochemistry showing the beta T-cell phenotype.

DISCUSSION

The non-specific components of the HLH-2004 criteria, combined with an often-severe clinical presentation, create a unique challenge for clinicians to differentiate HLH from other critical illnesses; for example, data on malignancy-associated HLH suggests that less than 50% of patients promptly received HLH-directed therapy due to diagnostic difficulty[4]. As such, early recognition of HLH is critical. With increasing recognition and diagnosis of adult HLH, there is greater understanding of disease characteristics and how varying etiologies influence patient outcomes[5,6]. Although adult treatment protocols are derived predominantly from pediatric data, new clinical trials have the potential to change future management of adult HLH, with drugs targeting INF-γ, CD-52, IL-1, and JAK-STAT in varying stages of testing[3,4].

In adult patients with newly diagnosed HLH, secondary HLH remains significantly more common than primary HLH5. While the most common etiology varies geographically, lymphoma represents the most common malignancy-related cause and overall secondary cause of HLH[4,5]. Since its initial description, SPTCL has been closely linked to hemophagocytic syndromes[7]. Representing approximately 1% of non-Hodgkin's lymphomas, it is highly associated with a rapidly progressive course of HLH[8]. Flow cytometry differentiates the α/β (SPTCL-AB) or γ/δ (SPTCL-GD) T-cell phenotypes, with SPTCL-AB usually following a more indolent course and conferring a better prognosis[8]. Treatment of SPTCL is variable but often includes steroids, other immunosuppressive agents, or cytotoxic chemotherapy[8,9].

A final diagnostic challenge was her clinical stability without disease progression over several months; findings such as colitis and regional lymphadenopathy initially suggested other causes. Despite her high HScore, it was challenging to definitively rule out infectious causes and commit her to cytotoxic therapy. Similar diagnostic dilemmas are likely responsible for the delayed diagnosis and treatment widely noted in other studies. As such, practitioners should have high clinical suspicion for secondary HLH in adult patients with appropriate disease markers and strongly consider workup for underlying malignancy.

CONCLUSION

As evidenced in this case, HLH is an uncommon syndrome that can be challenging to differentiate from other conditions causing multi-organ system dysfunction. Secondary HLH is significantly more common than primary HLH in adult patients, and malignancy (especially lymphoma) is the most common secondary etiology. Due to the non-specific diagnostic criteria for HLH and intense cytotoxic therapy, many patients experience delays in diagnosis and treatment.

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