A Rare Case of Hemophagocytic Lymphohistiocytosis Presenting in an Adult Patient

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) in adults is rare and presents diagnostic challenges due to nonspecific symptoms. Early recognition, multidisciplinary management, and timely intervention are critical to improving outcomes. This case underscores the need for improved awareness and specific treatment protocols for adult HLH. However, in this case, the treatment could not be started due to the patient's preference limited the case outcome.

Keywords: fever, hyperferritinemia, hemophagocytic syndrome, Secondary Hemophagocytic Lymphohistiocytosis

Introduction

HLH is a serious inflammatory condition that affects infants under the age of one, caused by various inherited disorders. However, in recent years, secondary forms of HLH have occurred more frequently in adults. HLH is caused by overactive natural killer cells and/or T lymphocytes, leading to an excessive number of cytokines in the bloodstream.[1] Adult HLH is rare, with a mean age of onset of 49 years and a male predominance of 63%, and 40–70% of cases are associated with malignancies. Its incidence is approximately 0.36 per 100,000 per year, with rates up to 2.8% in lymphoma patients and 9% in AML patients receiving intensive induction therapy.[1] The CD56 NK cells, which comprise 90% of the peripheral blood NK cells, have a high cytolytic capacity (cytotoxic), and secrete low levels of cytokines.[2] significant increase in percentage of CD56+ NK cells and NK cell activity after splenectomy in relapsed HLH patients.[3] Interleukin-10 (IL-10) is a key regulator of immune homeostasis.[4] As an immune-regulatory cytokine,[5] it is secreted by patients with HLH in large amounts of IL-10, which promotes the initial T cell differentiation to Th1 cells.[6] Elevated IL-10 levels were associated with lower platelet counts, and these two markers were independent risk factors for poor prognosis.[7] HLH causes activated T cells and macrophages to accumulate in vital organs, leading to tissue damage. It is usually caused by a perforin-mediated cytotoxic CD8+ cell and NK cell activity defect.[8] HLH has two types: primary (genetic) and secondary (caused by infections, malignancies, autoimmune diseases, or immune deficiency), which is the progression to HLH after treatment with the PD-1 blockader may occur,[9] as PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion.[10] Early treatment is important to avoid permanent tissue damage, but early diagnosis is often difficult, with many cases being misdiagnosed or undiagnosed.[11] Here, we present a rare and life-threatening case of hemophagocytic lympho-histiocytosis (HLH) in an adult patient, highlighting the diagnostic challenges, clinical progression, and the critical need for timely recognition and management to improve outcomes.

Case Report

A 52-year-old Indian man presented to the Emergency Department (ED) with fever, sweating, and upper back pain for one night. He had a history of incision and drainage of a furuncle on his upper back 3 days ago. There were no associated symptoms at that time. He is a known case of diabetes mellites but not complying with his medication. On examination, the wound appeared to be clean, with no signs of pus, erythema, or discharge. He was clinically stable with a stable vital sign reading except for the temperature of 39.4°C. The admitting clinician started him on an antibiotic, amoxicillin-clavulanate 1200mg three times a day and paracetamol as a pain killer. At the time, the laboratory parameters indicated suspicions of leukopenia, neutropenia, mild hypochromic microcytic anemia with anisocytosis, and the presence of a few large platelets (Table 1).

Table 1: Laboratory results.

Laboratory tests	Values	Normal values
WBC	2.1x10^3/uL	4-10x10^3/uL
RBC	4.2x10^3/uL	4.5-5.5x10^6/uL
Hb	11.6gm/dL	13-17gm/dL
Hct	33.5%	40-50%
MCV	80.7fL	83-101fL
Platelet	79x10^3/uL	150-410x10^3/uL
Neutrophils (%)	63.0%	
Lymphocytes (%)	29.4%	
Monocytes (%)	6.2%	
Eosinophils (%)	0.5%	
Basophils (%)	0.9%	
Urea	3.6mmol/L	2.5-7.8mmol/L
Creatinine	69umol/L	62- 106umol/L
Sodium	132mmol/L	133-146mmol/L
Potassium	3.8mmol/L	3.5-5.3mmol/L
Chloride	98mmol/L	95-108mmol/L
Bicarbonate	22mmol/L	22-29mmol/L
Magnesium	0.87mmol/L	0.70-1mmol/L
Bilirubin Total	12umol/L	0-21umol/L
Total protein	66gm/L	60-80gm/L
Albumin	34gm/L	60-80gm/L
Alkaline phosphatase	125U/L	40-29U/L
Alanine transaminase (ALT)	42 U/L	0-41U/L
Aspartate aminotransferase (AST)	34U/L	0-40U/L
C-reactive protein (CRP)	93.0mg/L	0-5mg/L
Ferritin	12,332ug/L	30-553ug/L
Iron	5umol/L	6-35umol/L
TIBC	40umol/L	45-80umol/L
Fe % saturation	12%	15-45%
Transferrin	1.6gm/L	2-3.6gm/L
HbA1C	12.2%	<5.7 - 6.4%
SARS-CoV-2 PCR	Negative	Negative
PT	11.7	9.4-12.5 seconds
APTT	55.2	25.1-36.5 seconds
INR	1.1	0.8 to 1.1
Fibrinogen	2.8 mmol/L	2.0 – 4.1 g/L
TGA	2.0 mmol/L	Normal: Below 1.7 mmol/L
Cholesterol	1.9 mmol/L	Desirable: Below 5.2 mmol/L
HDL	0.3 mmol/L	Normal: 1.0 mmol/L or

		above
IL-6	22 pg/mL	Less than or equal 7 pg/mL
IL-2R	17.07 ng/mL	1.2 – 8.80 ng/mL
Anti-Mitochondrial Ab	Negative	-
Anti-Smooth Muscle Ab	Negative	-
ANCA	Negative	-
ANA CTD	Negative	-

WBC;white blood cell, RBC;red blood cell; Hb;Hemoglobin; Hct;hematocrit; MCV;mean corpuscular volume; TIBC;total iron-binding capacity; SARS-CoV-2;severe acute respiratory syndrome coronavirus 2; PCR; polymerase chain reaction,PT ; Prothrombin time, APTT ; Activated prothrombin time, INR ; International normalized ratio, TGA ; Triglyceride, HDL ; High density lipoprotein, IL-6 ; Interleukin 6, IL-2R; Interleukin 2 receptor, ANCA ; antineutrophil cytoplasmic antibodies, ANA CTD ; Anti-Nuclear Antibody Connective tissue disease.

On the 3rd day of admission, the wound was clean, and cultures showed no growth. Clindamycin was started instead of the previous antibiotic. New blood, urine, stool, and parasite cultures were sent for investigation.

On the day 6th of admission, the patient continued to have spikes of fever of 39.5°C. HIV Ag/Ab was negative. Two days later, the urine culture showed positive for Candida tropicalis and Trichosporon asahii. Echocardiography showed normal results without vegetation, with LVEF of around 60% and hence Infective endocarditis were excluded. His Magnetic Resonance Imaging (MRI) showed normal results with no features that are suggestive of osteomyelitis or discitis. His Posterior chest wall ultrasound showed a small dorsal subcutaneous soft tissue lesion (known furuncle) with no deep communication extension or collection [Figure 1], and abdominal ultrasound (US) showed mild splenomegaly.

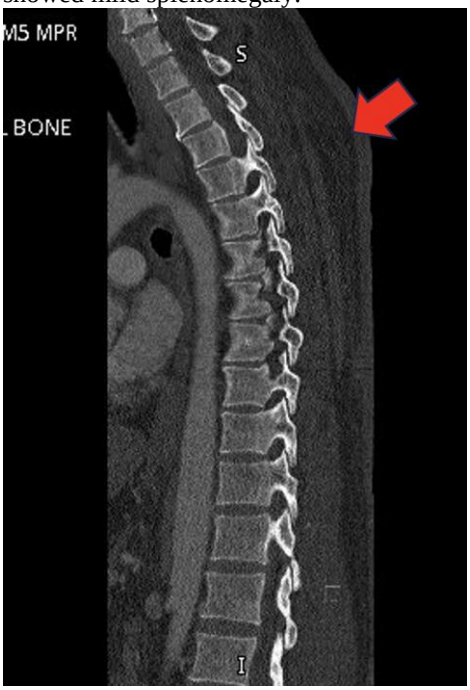

Figure 1: MRI Spine thoracic with contrast Dorsal subcutaneous soft tissue lesion (known furuncle) with no deep communication extension or collection and unremarkable same-level bony structures.

On the 11th day of admission, a noteworthy decline in C-reactive protein (CRP) levels was observed. The CRP levels, which had been consistently high at 93 since admission, began to show a downward trend, reaching 70 on

this day. Of note, the CRP levels had briefly dropped to 55 on day eight of admission. The patient's EBV PCR test results indicate a positive reading of 2,732 IU/mL, while the Autoimmune test yielded negative results. Additionally, the QuantiFERON TB test was negative, and the Parvovirus B19 Ab IgM test showed negative results, but the IgG resulted in positive results. Moreover, his antibiotic regime was clindamycin 450mg, and cefepime 2g three times a day was added to his regimen. The Computed tomography (CT) scan of the abdomen and pelvis showed normal tests with unremarkable findings, but the thorax showed some changes [Figure 2].

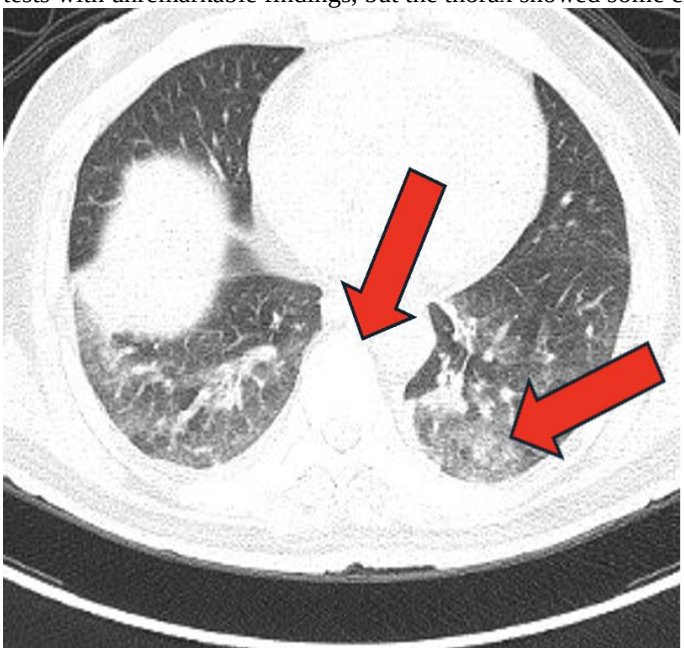

Figure 2: CT Thorax showing newly developed incomplete consolidation in both lower lung lobes dorso-basally.

On the 15$^{th\ day}$ of admission, the patient's tests showed negative for EBV Capsid IgM and positive for IgG. Hepatitis serology was negative. The patient had fluctuations in potassium and bicarbonate levels, which were corrected with potassium chloride, and continued to experience fevers [Figure 3]. LDH levels increased to 542 U/L, and ferritin levels rose to 12,332 ug/L. A bone marrow biopsy was recommended by the hematology team due to pancytopenia, persistent fever, and high ferritin levels to investigate the possibility of HLH. Malaria and virology panel tests were negative. Although thrombocytopenia is a common feature of hemophagocytic lymphohistiocytosis (HLH), other potential etiologies, such as autoimmune diseases, were screened and excluded. Additionally, the patient was not on anticoagulant therapy like aspirin or heparin, and there was no evidence of disseminated intravascular coagulation (DIC) during the clinical course.

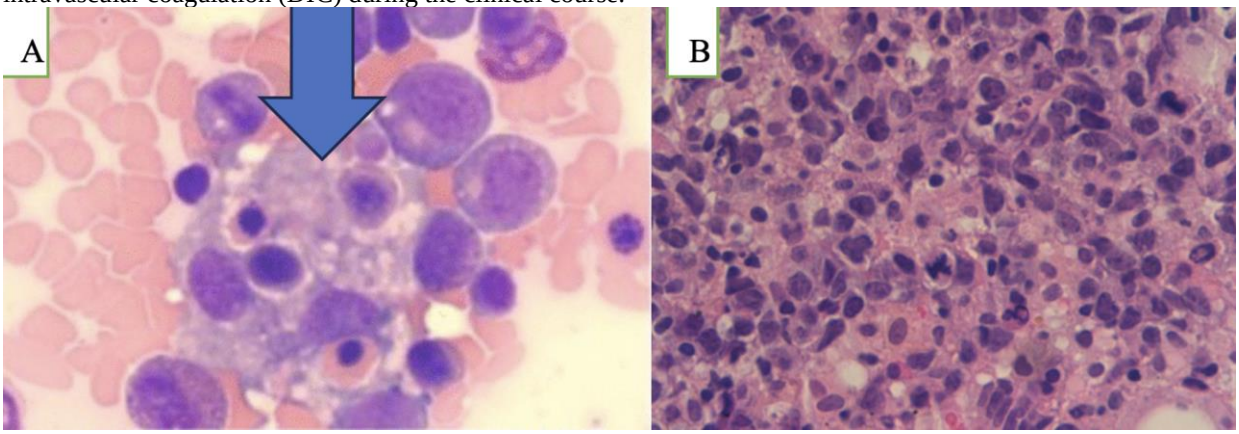

Figure 4: (A&B) Flow cytometry analysis shows approximately 7% of T-cells expressing CD3, CD5, and the majority expressing CD7, with a CD4:CD8 ratio at approximately 1.0. B-cells comprise 1% expressing CD19 & CD20 with a Kappa/Lambda ratio of approximately 1.7. The analysis also shows 1% polyclonal plasma cells expressing CD38/CD138 with a c K/L ratio of 0.9. The plasma cells are negative for CD56. The marrow shows variable cellularity (~ 30-55% cellularity) with active trilineage hemopoiesis and increased megakaryocytes with anisocytosis (blue arrow). CD68/ CD163 highlights increased cells of monocytic/histiocytic lineage and some with hemophagocytes. No lymphoid aggregate and no granuloma were noted.

On day twenty-one of his admission, his IL-2 was 17.07 ng/mL and IL-6 22 pg/mL. Then later, he underwent whole-body FDG PET CT (Whole-body positron emission tomography/computed tomography with the glucose analog 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG-PET/CT) showed new bilateral lung basal incomplete consolidation due to stasis and likely superimposed mild infection, increased adrenal uptake is likely due to hyperplasia, and No sign of FDG-avid malignancy, other focal infection, or lymphadenopathy was found [Figure 5].

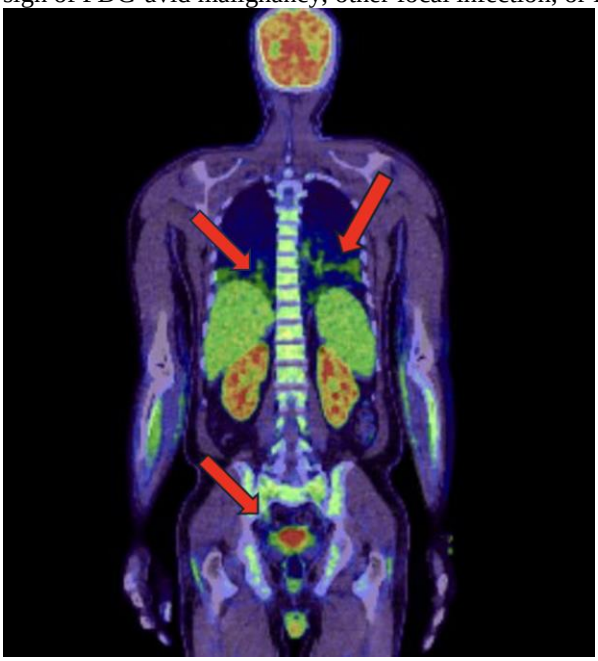

Figure 5: FDG-PET/CT showing newly developed incomplete consolidation in both lower lung lobes associated with minimal to mild FDG uptake. Bilateral adrenal glands present moderately increased uptake. Mild focal uptake corresponding to the recently excised left paravertebral furuncle.

After establishing HLH based on clinical and laboratory data and H score (Table 2), we prioritized quick and strong counseling with the patient, emphasizing the importance of rapid treatment due to HLH's significant morbidity and mortality risks. However, the patient wanted to return home for additional treatment. Even though we stressed the urgency and benefits of therapy in our facility, the patient insisted. Therefore, we explained the threats of delaying treatment and the potential for complications without immunosuppression. We advised the patient to see a hematologist upon arrival in his home country and gave him a thorough medical report, including biopsy results and detailed records. The patient was discharged against medical advice; thus, we could not start immunosuppressive medication. We wanted him to be ready for urgent treatment at home. We were willing to start immunosuppressive medication for HLH if the patient agreed.

Table 2: H score of our patient for Reactive Hemophagocytic Syndrome calculated using MDCalc.com.

Category	Score	Details
Result Summary	238	

Probability of Hemophagocytic Syndrome	98-99%	
Optimal Cutoff	169	Accurately classifies 90% of patients
Inputs		
Known underlying immunosuppression	0	No
Temperature, °F (°C)	33	101.1–102.9 (38.4-39.4)
Organomegaly	23	Hepatomegaly or splenomegaly
Number of cytopenias	34	3 lineages
Ferritin, ng/mL (or μg/L)	50	>6,000
Triglycerides, mg/dL (mmol/L)	44	132.7–354 (1.5–4)
Fibrinogen, mg/dL (g/L)	0	>250 (>2.5)
AST, U/L	19	≥30
Hemo-phagocytosis on bone marrow aspirate	35	Yes

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by excessive activation of macrophages and T cells, leading to multi-organ involvement. Although HLH is more commonly studied in pediatric populations, adult-onset HLH has been increasingly recognized, often triggered by infections, malignancies, or autoimmune disorders.[12] Infection-triggered HLH in adults can be precipitated by viral, bacterial, fungal, or parasitic pathogens, with viral triggers such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) being among the most frequently reported. Adult HLH typically presents with persistent fever, cytopenias, hepatosplenomegaly, and elevated ferritin levels, but the clinical picture is often nonspecific, contributing to delayed diagnosis and treatment.

Diagnosis of adult HLH is challenging due to the heterogeneity of clinical features and the lack of a universally validated adult-specific diagnostic standard. The HLH-2004 criteria, originally developed for pediatric patients, remain the most widely used diagnostic framework, requiring at least five of eight criteria or identification of a pathogenic HLH-associated gene mutation.[13] In adults, additional diagnostic tools can improve accuracy, including measurement of soluble CD25 (sCD25), natural killer (NK) cell activity, CXCL9, sCD163, CD18 expression, and genetic testing for HLH-associated mutations. Lumbar puncture can also be valuable in patients with suspected central nervous system involvement.[12, 14] The "H score" is another validated tool that incorporates laboratory and clinical parameters—such as cytopenias, ferritin, fibrinogen, fever, organomegaly, immunosuppression, and bone marrow hemophagocytosis—to estimate the probability of HLH in adult patients, with higher scores indicating near certainty of disease.[15]

In our patient, an H score of 238 corresponded to a 98–99% probability of HLH, and six of eight HLH-2004 criteria were met, including fever, splenomegaly, cytopenias, hyperferritinemia, and bone marrow hemophagocytosis. Extensive evaluation excluded alternative etiologies such as autoimmune disease, infective endocarditis, viral hepatitis, HIV, and malaria, confirming the diagnosis of HLH. Despite the clear indication for urgent therapy, the patient opted for discharge to continue care in their home country, illustrating a common therapeutic dilemma in adult HLH management: patients may refuse potentially life-saving interventions. Such

scenarios underscore the importance of early recognition, effective patient-centered counseling, and multidisciplinary discussion to optimize outcomes.[12]

Management of adult HLH remains challenging, and therapeutic strategies should be individualized according to the underlying trigger. Standard treatment often involves immunosuppressive therapy with dexamethasone and etoposide, with or without cyclosporine or intravenous immunoglobulin, while targeted therapies such as anti-cytokine agents (e.g., anakinra or emapalumab) are emerging for refractory or infection-triggered HLH.[12, 13, 16] In malignancy-associated HLH, particularly with non-Hodgkin's large B-cell lymphoma, controlling the underlying malignancy is essential, as malignant cells drive hypercytokinemia that triggers HLH. This case highlights the educational importance of recognizing adult-onset HLH, considering alternative diagnostic markers, and navigating therapeutic dilemmas, especially when patients decline treatment, to improve awareness and guide future clinical practice.[12, 17]

Conclusion

HLH is a rare but serious disease that can be life-threatening, especially in elderly and frail patients. It can be diagnosed by combining laboratory tests and instrumental data. Early intervention is crucial, and steroid treatment should be initiated promptly. If steroids don't work, aggressive supportive management is necessary, which may involve multi-immune suppressive drug protocols and interleukin-targeted therapies. However, an optimal regimen sequence still needs to be determined. Developing specific protocols for HLH patients is very important.

Disclosure

Written informed consent was obtained from the patient himself for the publication of this case report and any accompanying images.

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