Case report

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO COVID-19 ANDCHRONIC LYMPHOCYTIC LEUKEMIA MANIFESTED WITH QUOTIDIAN PYREXIA:A CASE REPORT

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening immune regulatory condition that can cause end-organ damage and death. HLH is clinically characterized by uncontrolled activation of cytotoxic T lymphocytes, natural killer cells, and macrophages that can lead to a cytokine storm. Fever, hepatosplenomegaly, cytopenia, elevated liver enzymes, hypertriglyceridemia, hyperferritinemia, andhemophagocytosis in the bone marrow, spleen, or lymph nodes are the hallmarks of the disease. Its primary (genetic) form is typically observed in pediatric patients and its secondary, acquired form is seen in adult patients with an underlying autoimmune, malignant, or infectious disease. Here, we present a case of secondary hemophagocytic lymphohistiocytosis in a 70-year-old male with a history of chronic lymphocytic leukemia who presented with persistent pyrexia of unknown origin (PUO).Diagnosis and management of HLH in adults are often extrapolated from the pediatric HLH-94 and HLH-2004 protocols. The management includes etoposide-based regimens containing corticosteroids, cyclosporine A, intravenous immunoglobulins (IVIG), intrathecal therapy, and liberal use of allogeneic stem cell transplant in higher-risk patients. Due to the diverse clinical manifestations and the presence of numerous diagnostic mimics, the diagnosis of HLH is challenging. Since the prognosis is typically poor, prompt diagnosis and

strong treatment are required. Here is a description of how our patient is diagnosed and treated based on the HLH 2004 protocol.

Keyword

Hemophagocytic lymphohistiocytosis, Macrophage activation syndromes,Chronic lymphocytic leukemia, COVID-19,Hyperferritinemia, Pyrexia of unknown origin,Thalidomide

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare life-threateninghyper-immunoinflammatorycondition characterized by immune activation and proliferation of cytotoxic T cells and macrophages leading to apotentially fatal cytokine storm that results in the engulfment of hematopoietic cells,malignant inflammation, andimmunosuppression resulting in multiple organ failure.[1,4]Primary or familial HLH is diagnosed primarily in the pediatric population and is usually caused byhomozygous mutations in the genes. About 40-60% of the mutations occur in PRF 1 and Unc-13 Homolog D (UNC13D) genes. Other genes involved are Syntaxin 11 (STX 11) and Syntaxin Binding Protein 2 (STXBP2), whereas secondaryor acquired HLH is common in adults and arises in patients with underlying infections [typically viral, such as Epstein-Barr virus(EBV), human immunodeficiency virus, and cytomegalovirus (CMV), but also bacterial, parasitic and fungal organisms], autoimmune/rheumatologic, malignant, or metabolic conditions. Epstein-Barr virus is the most common agent to cause HLH, which has poor outcomes. Left untreated, the dysregulated inflammatory response causes severe neutropenia, and patients often die from sepsis. The condition carries an increased rate of morbidity and mortality. [2,3,6,5]

Presentation of Case

A 70-year-old male patient came to the hospital with complaints of recurrenthigh-gradefever spikesand generalized fatigue. The patient had a history of Chronic lymphocytic

leukemia (CLL) and received multiple cycles of bendamustine/rituximab and achievedcomplete remission. During hospitalization, he was detected with EBV and CMV and was treated with Ganciclovir. He had fever-triggeredseizures and is on antiepileptics. He was also detected with pulmonary aspergillosis infection which was treated with amphotericin B. He had a history of multiple episodes of severe chronic COVID-19, and he received a high dose of monoclonal antibodies (Casirivimab + Imdevimab 2400mg each) after which fever gradually subsided. However, because of his severe immunocompromised state and the potential for persistent viremia, he also received another dose of monoclonal antibodies (1200mg each).

Considering the possibility of persistent viremia and his severe immunocompromised status, he was administered another dose of monoclonal antibody (1200mg each). After which his fever settled.

Four months back he was diagnosed with disseminatedTuberculosis (TB) and was on Antitubercular therapy (ATT). While on therapy he got rifampicin-induced hepatomegaly and increased liver enzymes because of which the drug was withheld and given levofloxacin. Later the patient was diagnosed with Pyrexia of unknown origin (PUO) and treated with Thalidomide 100mg. The patient did not tolerate the medicine and continued to have a high-grade fever with reduced appetite.

On admission, his initial vitals were blood pressureof 110/60 mmHg, pulse rate of 120/min, SPO2 of 97%, and temperature of 102^0 F. During physical examination, he was found to have axillary lymph node enlargement and tachycardia.

Table 1 Laboratory tests at admission showing pancytopenia, the elevation of liver tests, and CRP

[PCV: Packed cell volume, TLC: Total leukocyte count, CRP: C-reactive protein, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transferase,

PT: prothrombin time, INR: International normalized ratio, PTT: Partial thromboplastin time]

Parameters	Observed values		Reference range
Haemoglobin	6.8	↓	13.0 - 17.0 g/dL
PCV	22	↓	40 - 50 %
TLC	192	↓	4000 - 11,000 cells/mm^3
Neutrophils	83.3	↑	40 - 80 %
Platelets	1,33,000	↓	1,50,000 - 4,50,000 cells/mm^3
CRP	247	↑	< 0.5 mg/dL
Sodium	124	↓	136 - 145 mmol/L
Potassium	4.13		3.5 - 5.1 mmol/L
Blood Urea	31		13 - 43 mg/dL
Creatinine	0.74		0.9 - 1.3 mg/dL
AST	72	↑	< 35 U/L
ALT	49	↑	< 34 U/L
GGT	463	↑	< 55 U/L
Total Protein	5.4	↓	6.4 - 8.3 g/dL
Albumin	2.7	↓	3.5 - 5.2 g/dL
Alkaline Phosphatase	647	↑	53 - 128 U/L
Ferritin	13548	↑	20 - 291 ng/ml
Triglycerides	198	↑	< 150 mg/dL
Lactate	318	↑	120 - 246 U/L

dehydrogenase			
Procalcitonin	2.99	↑	< 0.5 ng/ml
Plasma Fibrinogen	600	↑	200 - 393 mg/dL
D-dimer	1448	↑	< 500 ng/dL
PT	14.2	↑	11.1 - 12.9 sec
INR	1.18	↑	0.8 - 1.2 sec
PTT	42	↑	26.3 - 32.2 sec

Routine clinical evaluation revealed pancytopenia and neutropenia.Because of the neutropenic sepsis possibility,the patient was started on empirical antibiotics (Inj.Meropenem 1gm and Inj.Teicoplanin 400mg), Inj. G-CSF 300mg and other supporting measures.The patient was also started on a combination of sulfamethoxazole 800mg and trimethoprim 160mg, prophylactic antifungal (Inj.Posaconazole 300mg), and antiviral (Inj.Valacyclovir 1gm). Dermatologic opinion was obtained for developing a single crusted lesion over the right angle of the mouth which was found to be herpes facialis which was treated with Mupirocin ointment for 5 days.

An axillary lymph node biopsy was done suggesting HLH. Additional studies on the marrow noted a prominent population of CD68+ macrophages with active hemophagocytosis. These findings in combination with cytopenia led to further studies revealing high serum ferritin levels,hypertriglyceridemia, hyponatremia, hyperfibrinogenaemia, natural killer (NK) cell depletion, and elevation of the soluble cluster of differentiation (CD)25 (>5000/uL).Because of all these findings and after ruling out the possibilities of sepsis / active infective etiology the patient was diagnosed with secondary HLH.

Thepatient was then initiated on pulse steroid therapy (Inj. Methylprednisolone) for 3 days and was changed to oral steroid. It showed a minimal response and became symptomatic with

total counts in decreasing trends. Therefore, the patient was started on chemotherapy with etoposide and dexamethasone after premedication. The patient tolerated well and fever spikes settled and clinically improved.

Discussion

HLH isa highly detrimental syndrome characterized by a rapidly progressive clinical course and a high mortality rate with a median survival of about two months. The disease is sporadic, with an incidence of about 1-2 cases per million in adults and a survival rate of <10% in the pre-immuno-chemotherapeutic era. [(7)]

The most common clinical manifestations include fever, hepatosplenomegaly, serous cavity effusion, and central nervous system (CNS) symptoms. With the progression of the disease, multiple organ infiltration by the activated T cells and macrophages occurs, ultimately leading to multiple organ damage.[(8)]

The diagnosis is based on HLH-2004 diagnosis criteria in conjunction with clinical judgment and the patient's history. The HLH-94 protocol proposed a standardized set of five diagnostic criteria for HLH. These were revised for the HLH-2004, and it was established that individuals need to meet five or more of the eight diagnostic criteria presented in Table 2.

Table 2HLH-2004 Diagnostic Criteria[(9)]

If either condition A or condition B is true, the diagnosis of HLH can be made:
A. A molecular diagnostic that supports HLH
B. Any 5 of the eight clinical and laboratory standards for HLH listed below:
1. Fever >38.5 °C
2. Splenomegaly
3. Cytopenia, which affects about two of the three lineages in peripheral blood
Hemoglobin level of 9 g/dL (for newborns 4 weeks: 100 g/L)

Neutrophils: 1.0 109/L

Platelets: 100 109/L

4. Fasting triglycerides >3.0 mmol/L (>265 mg/dL) or fibrinogen 1.5 g/L: hypertriglyceridemia and/or hypofibrinogenemia

5. Hemophagocytosis in the lymph nodes, bone marrow, spleen, liver, or other tissues

6. Natural killer (NK) cell activity is either low or absent.

7.Ferritin concentration in serum 500 g/L

8. Soluble CD25 (soluble IL-2 receptor), 2400 U/mL.

Thediagnosis of HLH in our patient was based on the HLH-2004 criteria [11] i.e., our patient presented seven out of eight criteria: persistent fever,cytopenia, hyperferritinemia, hyperfibrinogenaemia, altered liver enzymes, hypertriglyceridemia, CD68+ macrophages with active hemophagocytosis, diminished NK cell activity, and an elevated soluble CD25.

Table 3 Parameters Included in the Adapted HLH-2004 Guidelines and H-Score and the Number of Points Associated with Each Criterion for Scoring

Parameter	Adapted HLH-2004 Guidelines	H-Score
Fever (°C)	0 (<38.5) or 1 (≥38.5)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Splenomegaly	0 (no) or 1 (yes)	
Organomegaly		0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
Cytopenia	0 (one lineage) or 1 (two or three lineages)[b]	0 (one lineage), 24 (two lineages), or 34 (three lineages)[c]
Ferritin (ng/mL)	0 (<500) or 1 (≥500)	0 (<2,000), 35 (2,000-6,000), or 50 (>6,000)
Triglycerides (mmol/L)	0 (<3) or 1 (≥3)	0 (<1.5), 44 (1.5-4), or 64 (>4)
Fibrinogen (g/L)	0 (>1.5) or 1 (≤1.5)[d]	0 (>2.5) or 30 (≤2.5)
Hemophagocytosis in bone marrow	0 (no) or 1 (yes)	0 (no) or 35 (yes)
Aspartate aminotransferase (IU/L)		0 (<30) or 19 (≥30)
Known underlying immunosuppression		0 (no) or 18 (yes)

HLH, hemophagocytic lymphohistiocytosis.
[a]Data are presented as number of points, with values in parentheses.
[b]Defined as hemoglobin less than 90 g/L, platelets less than 100×10^9/L, and neutrophils less than 1.0×10^9/L.
[c]Defined as hemoglobin 92 g/L or less, platelets 110×10^9/L or less, and leukocytes 5×10^9/L or less.
[d]The point is not added if there is already one point for triglycerides.

Adapted from

#https://www.researchgate.net/publication/303949258_Performances_of_the_HScore_for_Diagnosis_of_Hemophagocytic_Lymphohistiocytosis_in_Adult_and_Pediatric_Patients

An H-Score for reactive hemophagocytic syndrome of 246 points was calculated, meaning that the probability of hemophagocytic syndrome was greater than 99%.

The HLH-94 protocol consists of eight weeks of induction therapy with dexamethasone and etoposide, followed by eight weeks of continuous therapy with dexamethasone, etoposide, and cyclosporine, which is appropriate in the case of disease relapse or primary HLH. Cyclosporine was encouraged to be included during the induction phase of the procedure when it was amended in 2004. [9,11,12]

In this clinical scenario, our patient was started on chemotherapy with etoposide and dexamethasone. The patient tolerated well and clinically improved.

Conclusion

Hemophagocytic lymphohistiocytosis is an acute hyperinflammatory disease associated with a high mortality rate and poor prognosis. So,we would like to emphasize the challenges of diagnosing and managing HLH, especially in elderly and frail patients. The physicians must possessa reasonable index of suspicion for HLH in any patients with fever, pancytopenia, high ferritin levels, and low fibrinogen levels, themanagement requires rapid diagnosis using a multidisciplinary strategy, including chemotherapy, immunosuppression, supportive care, and therapy for the underlying causes.Diagnostic criteria and treatment protocolsspecific to adult Hemophagocytic syndrome (HPS) have not been established and are often extrapolated from the Histiocyte Society's HLH-94 or 2004 pediatric protocols. Several described manifestations of adult HPS, such as transaminitis, coagulopathy, elevated LDH, rash, hyponatremia, elevated CRP, and neurologic involvement,are not included in these criteria. It is unclear how well these therapy regimens work for adults. Priorities for future research include the development of diagnostic criteria and treatment protocols that accommodate those disease aspects unique to adults.

Consent

Writteninformed consent was obtained from the patient regarding the publishing of his anonymizedclinicaland Para clinicaldatain the current study.

EthicalApproval

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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