第 49 卷 第 10 期
2022 年 10 月

湖南大学学报（自然科学版）
Journal of Hunan University (Natural Sciences)

Vol. 49 No. 10
October 2022

Open Access Article https://doi.org/10.55463/issn.1674-2974.49.10.13

A Case Report of Hemophagocytic Lymph Histiocytosis in a Young Male

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Abstract: Hemophagocytic Lymph Histiocytosis (HLH) is a clinical syndrome affected by excessive immune stimulation and tissue hyperinflammation, which is relatively underdiagnosed because of its various clinical manifestations. This case described a young male whose body temperature measured at 39°C and only dropped briefly due to a fever reducer. He had a painless inflammation in the neck during the fever. Cold and stuffy nose emerged before the fever appeared. Moreover, stuffy nose caused snoring sleep. The patient also faced bleeding gums and nosebleeds. However, he did not experience body ache or weight loss. Various clinical tests, such as clinical chemistry laboratory tests, blood and bone marrow tests, and radiological tests were conducted. Clinical chemistry test revealed a decrease in albumin levels. Additionally, peripheral blood test showed a smear of microcytic hypochromic anemia, leukopenia and thrombocytopenia, while bone marrow examination showed a process of hem phagocytosis/metabolic disease. Furthermore, radiological tests showed no abnormalities.

Keywords: hemophagocytic lymph histiocytosis, immune stimulation, tissue hyperinflammation, young male.

青年男性噬血细胞性淋巴组织细胞增生症一例

摘要：噬血细胞性淋巴组织细胞增生症（HLH）是一种受过度免疫刺激和组织过度炎症影响的临床综合征，因其临床表现多样而相对漏诊。该病例描述了一名年轻男性，其体温测量为 39 摄氏度，并且由于退烧药而仅短暂下降。发烧期间，他的颈部出现了无痛性炎症。在发烧出现之前就出现了感冒和鼻塞。此外，鼻塞导致睡眠打鼾。患者还面临牙龈出血和流鼻血。然而，他并没有感到身体疼痛或体重减轻。进行了各种临床测试，例如临床化学实验室测试、血液和骨髓测试以及放射学测试。临床化学测试显示白蛋白水平下降。此外，外周血检查显示小细胞性低色素性贫血、白细胞和血小板减少的涂片，而骨髓检查显示有血细胞吞噬/代谢性疾病过程。此外，放射学检查未见异常。

关键词：噬血细胞性淋巴组织细胞增多症，免疫刺激，组织过度炎症，年轻男性。

1. Introduction

Hemophagocytic Lymph Histiocytosis (HLH) is a clinical syndrome affected by excessive immune stimulation and tissue hyperinflammation, which is relatively underdiagnosed because of its various clinical manifestations. Hemophagocytic Lymph histiocytosis is sporadic or familial, which is generally triggered by precipitation, including infection or malignancy. Chemotherapy has been proved as a highly effective treatment in controlling and curing HLH, even in prolonging survival. Hemophagocytic Lymph histiocytosis attacks either male or female with

Received: July 10, 2022 / Revised: August 7, 2022 / Accepted: September 4, 2022 / Published: October 30, 2022

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a reported incidence of 1 in 3000 in hospitalized children. A positive previous case of a family member, such as a parental relationship and the death of a sibling is supposed to be a major clue due to the autosomal recessive nature of inheritance. Early diagnosis of this rare yet fatal condition is very crucial because the spectrum of clinical presentation varies including simple fever to organomegaly, cytopenia and sometimes advanced organ damage [1]-[2].

Hemophagocytic lymph histiocytosis is classified based on its etiology. The differentiation of primary histiocytosis from the secondary is essential because the management of therapy differs depending on its type. Primary Hemophagocytic Lymph histiocytosis emerged in the pediatric age group, while the secondary lymph histiocytosis commonly appeared in adults and the elderly group. The genetic form of HLH can be divided into Familial HLH (FHLH) associated with immunodeficiency syndrome and asymptomatic [1]-[2].

2. Case Report

2.1. Patient Identity

Name: IKAW
Identity Number: 21060647
Gender: Male
Age: 7 years old
Date of birth: April 23rd, 2014
Address: Jl. Kartika Plaza gg. Samudra No. 3, Kuta, Badung
Date of treatment: November 10th, 2021

2.2. Anamnesis

Fever.

2.3. Current Illness

He was a referral patient from another hospital who had been facing fever for 2 weeks before being referred to the RSUP. His body temperature measured at 39°C, which only drop briefly by using fever reducer, later it rose again. He had a painless inflammation in the neck during the fever. A cold and stuffy nose emerged before the fever appeared (about 3 weeks before referring to the RSUP). Moreover, stuffy nose caused snoring sleep. The patient also faced bleeding gums and nosebleeds. However, he did not experience body ache or weight loss.

2.4. Past Medical History

Previous similar diseases were argued.

2.5. Family Health History

Family members do not have hypertension, diabetes, heart disease, asthma and allergies. His family members were not identified with similar illness.

2.6. Physical Examination

General condition: Moderate
GCS: E4V5M6
Blood pressure: 100/60 mmHg
Pulse: 94 times/minute
Breathing: 22 times/minute
Temperature: 38.8°C
Head: Anemia +/+, icteric -/-, palpebral edema -/-
Neck: Multiple enlargements in the area of coli dextran et sinistra, diameter 2 cm, fixed soft, no tenderness, no hyperemia.
Cor: S1-S2 normal, regular, murmur (-)
Pulmo: vesicular +/+, rhonchi -/-, stridor during sleep+/+
Abdomen: distension (-), bowel sounds (+) normal, ascites (-), tenderness (-), liver palpable 1 finger below the costal arc, spleen palpable Scuffner II, mass not palpable
Extremities: warm acral, edema (-)

2.7. Supportive Check Up

The patient faced several supporting check-ups, including:

2.7.1. Hematology Laboratory Check-Up

During a complete blood check-up, the results of leukopenia, anemia, and thrombocytopenia are shown in Table 1.

Table 1 Complete blood test results

Parameter	10/11/2021	16/11/2021	20/11/2021	23/11/2021	Reference Value
WBC (10^3/µL)	1.15	0.86	0.60	0.48	6.0 - 14.0
% Neu	22.70	18.60	15.00	4.10	18.30 - 47.10
% Lymm	73.00	72.10	81.70	93.80	30.00 - 64.30
% Mono	4.30	9.30	3.30	2.10	0.0 - 7.10
% Eos	0.00	0.00	0.00	0.00	0.0–5.0
% Baso	0.00	0.00	0.00	0.00	0.0-2.0
RBC (10^6/µL)	3.08	3.16	2.06	1.25	4.10 - 5.3
HGB (g/dL)	7.20	7.60	5.30	3.40	12.0 - 16.0
HCT (%)	21.70	22.60	15.20	9.70	36.0 - 49.0
MCV (fL)	70.50	71.50	73.80	77.60	78.0 - 102.0
MCH (pg)	23.40	24.10	25.70	27.20	25.0 (g 35.0
MCHC) /dL)	33.20	33.60	34.90	35.10	31-36
RDW (%)	16.40	17.60	18.20	19.90	11.6 - 18.7
PLT (10µ/µL)	38.00	33.00	8.00	18.00	140 - 440

Continuation of Table 1					
NLR	0.31	0.26	0.18	0.04	≤ 3.13

On hemostasis physiology check-up, pathological hemostasis was impaired intrinsic, extrinsic and shared stages, as shown in Table 2.

Table 2 Results of hemostasis physiology check-up

Parameters	**10/11/2021**	**16/11/2021**	**23/11/2021**	**Referral Value**
(Seconds)	13.0	18.2	13.7	10.8-14.4
INR	1.16	1.31	1.22	0.9-1.1
APTT (seconds)	43.3	47.9	45.1	24-36

2.7.2. Clinical Chemistry Laboratory Test

Clinical Chemistry test revealed a decrease in albumin levels, an increase in levels of *Lactate Dehydrogenase* (LDH), procalcitonin, *aspartate aminotransferase* (AST), *alanine transferase* (ALT), total bilirubin, direct bilirubin, triglycerides, and ferritin, as shown in Table 3.

Table 3 Results of clinical chemistry test

Parameters	**11/11/2021**	**23/11/2021**	**Reference Value**
LDH (U/L)	2398		240 - 480
Procalcitonin (ng/mL)	2.72	21.28	< 0.15
AST (U/L)		809.9	5 - 34
ALT (U/L)		120.70	11 – 50
Albumin (g/dL)		2.07	3.40 - 4.80
Glucose while (mg/dL)		84	70 – 140
Total Bilirubin (mg/dL)		8.74	0.30 – 1.20
Direct Bilirubin (mg/dL)		6.80	0.00 – 0.50
Indirect Bilirubin (mg/dL)		1.94	
Triglycerides (mg/dL)		413.8	< 150
Ferritin (ng/mL)		33511.20	21.81 - 274.66 Peripheral

2.7.3. Blood and Bone Marrow

1) Peripheral Blood Test

Erythrocytes: Microcytic hypochromic, poikilocytosis (positive ovalocytes, tear cells) drop positive), negative polychromasia cells, negative normoblasts.

Leukocytes: Impression of decreased number, differential count neutropenia, negative toxic granules, negative vacuolization, no young cells found.

Platelets: The impression of a decreased number, negative giant platelets, negative clumping.

Impression: Microcytic hypochromic anemia, leukopenia (neutropenia), and thrombocytopenia.

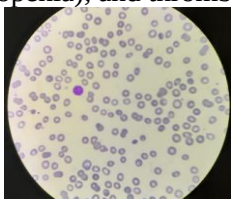


Fig. 1 Peripheral blood smear with 1000x magnification

The test showed a smear of microcytic hypochromic anemia, leukopenia (neutropenia) and thrombocytopenia.

2) Bone Marrow Test

Cellularity: Slightly hypocellular

Erythroid System: Decreased

Myeloid System: Normal, Myeloblast 3%

Megakaryocyte System: Decreased Activity

Other Cells: Large cells resembling macrophages with hemphagocytosis were found.

Conclusion: Bone marrow examination shows the process of hemophagocytosis dd/ *metabolic disease*.

Suggestion: Please do other clinical and laboratory evaluation.

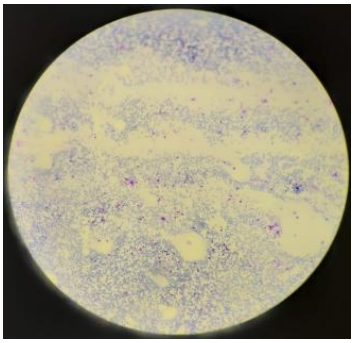
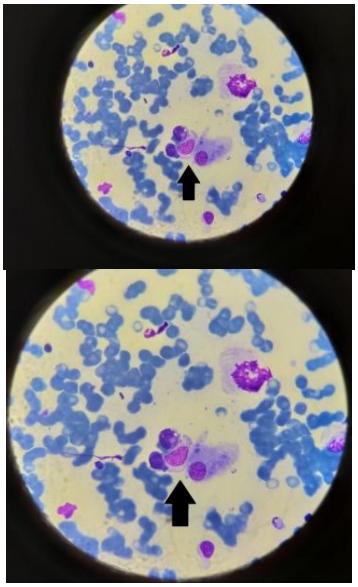


Fig. 2 Bone marrow image with 100x magnification

There is a picture of hypocellularity in bone marrow preparations.



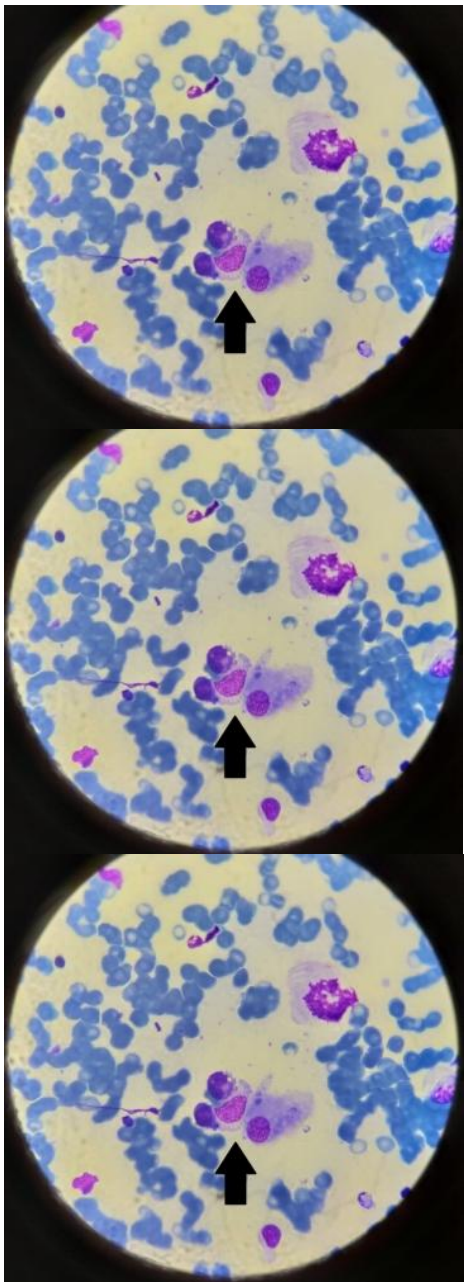


Fig. 3 Bone marrow image with 1000x magnification

Macrophages appear to eat other cells in the vicinity.

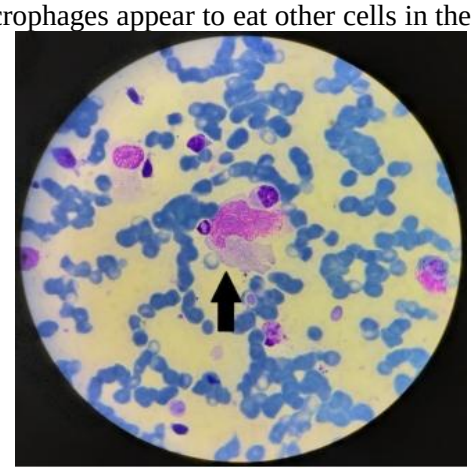


Fig. 4 Hemophagocytosis on a bone marrow image with 1000x magnification

Macrophages appear to eat other cells in the vicinity.

2.7.4. Radiological Test

1) Chest X-ray AP (15/11/2021)

Impression: Cor does not show any abnormalities. Pneumonia susp pneumonic metastatic type. Obs right hilar thickening, hilar susp lymphadenopathy.

2) Photo Waters (17/11/2021)

Impression: Bilateral inferior concha nasi hypertrophy. No visualized fractures and dislocations of bones and joints.

3) Thyroid Ultrasound (22/11/2021)

Impression: Multiple suspicious lymphadenopathies of the coli region, submandibular, submental, to the right and left parotid. a right left thyroid, isthmus, submandibular gland and right and left parotid, no abnormalities were observed.

2.8. Working Diagnosis

Hemphagocytosis Lymphhistiocytosis.

2.9. Treatment Management

The patient was treated as follows:

a. Nasal cannula O_2 3 liters/minute
b. Dexamethasone 5 mg/ml injection
c. Methylprednisolone 125 mg injection
d. Paracetamol 1g/100ml infusion
e. Paracetamol syrup 60 ml 120 mg/5 ml
f. Prednisone 5 mg tablets
g. Cefepime 1g injection
h. Omeprazole 40 mg/10 ml
i. Avamys injection (fluticasone) intranasal spray
j. Phytomenadione (vitamin k1) 2 mg/ml injection
k. IVFD injection Nacl 0.9% 10 tpm

3. Discussion

Hemophagocytosis is the ingestion of cellular blood components and their precursors by macrophages, resulting in cytopenia. Hemophagocytic Lymph histiocytosis is characterized by an uncontrolled and ineffective immune response, triggered due to various causes such as malignancy, infection and some autoimmune disorders leading to severe hyperinflammation and fatal multiple organ damage. The clinical symptoms of HLH include fever, hepatosplenomegaly, lymphadenopathy, pancytopenia in peripheral blood, hypertriglyceridemia, hypofibrinogenemia, increased ferritin levels, increased transaminase enzymes and bilirubin in the blood and abnormalities in neurological function [2]-[4].

During the anamnesis stage, previous fever had emerged since the latest 2 weeks, the patient felt a painless swelling in the neck, cold and stuffy nose since before the fever appeared and affected in causing snoring sleep due to the nose was blocked. The literature suggests that HLH should be suspected in cases of *systemic inflammatory response syndrome* (SIRS), including fever, malaise, hepatosplenomegaly,

jaundice, lymphadenopathy, and cytopenia [5].

The patient's complete blood test revealed that the patient had leukopenia, anemia, and thrombocytopenia (pancytopenia). Pancytopenia in HLH patients is affected by increased macrophage production. This increase in macrophage production was caused by the suppression of hemopoiesis by increasing the levels of inflammatory cytokines such as IFN-α released by activated T cells, then a hem phagocytosis process occurs, where macrophages phagocytize or destroy blood cells such as erythrocytes, leukocytes and platelets as compensation [6]-[7].

The patient's test of hemostasis showed prolongation of the PPT and APTT. PPT examination is a marker for assessing hepatic synthesis function because almost all coagulation factors are synthesized in the liver except factor VII. In patients with severe liver damage, the synthesis of coagulation factors by the liver is reduced so that the PPT will be prolonged, then along with the worsening of the disease, the APTT will also be prolonged. It is stated that patients with HLH can experience attacks of organs, such as the liver, causing damage to the liver.

Based on clinical chemistry test, levels of LDH, procalcitonin, AST, ALT, total bilirubin, direct bilirubin, triglycerides and ferritin showed an increase. This patient also had a decrease in albumin levels. Elevated LDH levels in HLH patients are thought to be caused by cellular injury resulting from multiple organ damage. Elevated AST and ALT were caused by damage to hepatocytes. AST is present in the mitochondria and hepatocyte cytosol, whereas ALT is present only in the hepatocyte cytosol. Increasing levels of ALT and AST were caused by *acute liver failure*, which can occur as the most common complication in HLH patients, as one of the effects of multi-organ failure in the HLH progression. Although the mechanism of *liver injury* in HLH patients is not known with certainty, it is thought to be related to the infiltration of excessively activated hemophagocytes into all cells or excessive cytokine production [8].

Elevated procalcitonin levels in these patients are predicted happen due to bacterial infection or in other infections that can activate cytokine release, including fungal, malarial infections and in patients who are taking drugs that stimulate cytokine release, such as OKT3, antilymphocyte globulin, and alemtuzumab. The increase in bilirubin in HLH patients is determined by liver cell damage, causing the bilirubin conjugation process disruption and a decrease in the rate of bilirubin absorption by liver cells. The mechanism for increasing both total and direct bilirubin in HLH patients is not known for sure, but it is related to excessive infiltration of activated hemophagocytes into all cells or excessive cytokine production [8]-[9].

Moreover, the elevation of triglyceride levels can also be found in these patients. The mechanism of increased triglyceride levels is not detected for certain, but it is suspected that hypertriglyceridemia in HLH is caused by decreased lipoprotein lipase activity triggered by increased levels of *Tumor Necrosis Factolls* and sCD25 were not tested because of the high cost of the test, not available in all laboratories, and the time-consuming expectation of the test results. It is important to examine *NK cells* and sCD25 considering that in several studies, the sensitivity of the two tests is around 93-95%. Other molecular tests, such as mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4, should be performed to classify patients with primary or secondary HLH because they are associated with the initial and continued therapy of this HLH.

The patient was initially referred to another hospital with facing of long-standing fever since the latest 2 weeks before referring to the RSUP, with swollen glands with each fever. A complete blood test was performed with the results of pancytopenia and on November 11, 2021, a peripheral blood smear was performed with the results of microcytic hypochromic anemia, leukopenia (neutropenia) and thrombocytopenia. Then, on November 16, 2021, a BMA procedure was performed out with the impression that the bone marrow image reading showed a process of hem phagocytosis dd/metabolic *disease.* On November 20, 2021, the patient's condition worsened, marked by fever > 39°C, swollen glands that caused the patient to have shortness of breath and bleeding from the gums. On November 24, 2021, the patient died with a suspected cause of gastrointestinal bleeding.

Diagnosing HLH is an important first step toward successful therapy but is challenging because of the rarity, variable presentation, and nonspecific findings of HLH. Based on [16], it was estimated that there was 1 case of HLH per 3000 inpatient admissions in a tertiary care pediatric hospital. Practical considerations for diagnosis include rapid assessment and recognition of signs of HLH, particularly in patients with severe and critical clinical signs. Based on previous studies, sCD25 is one of the most useful markers of inflammation, as it correlates with current disease activity more consistently than ferritin or other disease indices. However, ferritin can also be a useful marker because levels > 10,000 g/dL are very sensitive and specific for the diagnosis of HLH and the sCD25 test is not available in all laboratories. Because hem phagocytosis is neither sensitive nor specific for HLH and not all patients develop hem phagocytosis at any onset, hem phagocytosis is considered one of the less important diagnostic criteria. The same diagnostic and therapeutic approaches apply for both children and adults, although special care should be exercised in treating adults as they may experience significant comorbidities, particularly associated with high-dose

steroid therapy [5], [16].

Generally, HLH treatment uses symptomatic therapy, immunosuppressant and *modulatory agents*, biological response modifiers, treatment of co-morbidities, and *subsequent stem cell transplantation*. Therapy is aimed at suppressing the hyperinflammatory state and immune dysregulation that leads to further organ damage and susceptibility to lethal infection. HLH treatment may vary according to the cause. Treatment is divided into FHL, infectious, malignancy-related, and autoimmune diseases [10].

4. Conclusion

Hemophagocytic Lymph Histiocytosis (HLH) is a clinical syndrome due to excessive immune stimulation and tissue hyperinflammation that is relatively underdiagnosed due to its varied clinical manifestations. The handling process of HLH depends on the clinical symptoms and the type of HLH. A complete and adequate supporting medical check-up greatly influences the diagnosis of HLH. Complete blood count, peripheral blood smear, ferritin, triglycerides, bone marrow aspiration, and fulfillment of the diagnostic criteria for HLH are basic examinations for establishing the diagnosis of HLH. Additional specific tests such as NK cells and sCD25 mutations PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 can be performed if necessary.

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