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International Journal of Clinical Surgery

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Case Report

Haemophagocytic Lymphocytosis (HLH) Vicious Cycle in a Cannabinoids Addict Patient Case Report and Disease Review

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Received Date: October 10, 2022; Accepted Date: October 23, 2022; Published Date: October 31, 2023

Citation: Eman M. Frrag, Hiba Hamdar, Amro E. Amer, Ahmed E. Amer, Abdalla M. Hadhoud, et al., (2023), Haemophagocytic Lymphocytosis (HLH) Vicious Cycle in a Cannabinoids Addict Patient Case Report and Disease Review. *International Journal of Clinical Surgery* 2(5); DOI:10.31579/2834-5118/033

Abstract

Introduction: Haemophagocytic lymphocytosis (HLH) is a rare life-threatening syndrome caused by the uncontrolled activity of cytokines, natural killers, and macrophages, which can alter the activity of the organism, resulting in multiple organ dysfunction and mortality. Fever, splenomegaly, coagulopathies, dyspnea, changes in mental status, or irritability may be associated with HLH diseases. Depending on the underlying causes, such as bacterial or viral infections, HLH may be primary, hereditary, or secondary. The early diagnosis and treatment of patients are directly related to their prognosis and clinical outcome. On the other hand, HLH can present a number of obstacles, particularly for children and newborns, as well as hematological defects which might cause other autoimmune disorders.

Case presentation: We present a case of a 28-year-old male patient admitted to the hospital with a history of persistent high grade fever for two weeks, right lower limb swelling three weeks prior to admission, and right side weakness for one month. Aside from being addicted to cannabis for three years, the patient has no prior medical history. On admission, the patient was awake, conscious, oriented, and hemodynamically stable. A complete blood count, ultrasound examinations, and a whole-body CT scan revealed that the results were favorable for multiple enlarged lymph nodes and hepatosplenomegaly. The patient was given acyclovir, Vfend, Colistin, Targocid, Tinam, Septrin, and anticoagulant during the follow-up. The patient's clinical condition was rapidly deteriorating; a bone marrow biopsy was performed, which revealed haemophagocytosis; and dexamethasone was started. The patient's clinical condition deteriorated during his hospital stay until he went into cardiac arrest and had to be resuscitated for 30 minutes with pulseless electrical activity.

Background and Aim: This case suggests that we should be vigilant to the patient who is admitted to the hospital with symptoms for unknown reasons, in order to diagnose HLH as soon as possible and clarify its cause, and it also puts several theories regarding the pathogenicity of this disease in our hands, which will be described in this case, making this case a subject for discussion and research in the medical field.

Conclusion: Haemophagocytic lymphocytosis (HLH) is a severe inflammatory disease that improperly controls the body's immune response. Viruses and bacterial infections are just two examples of the various etiological causes that can cause it. Lab results and symptom presentations that are particular to the primary infection can indicate it. Diagnosis and treatment must be provided as soon as possible in order to reduce morbidity and mortality.

Keywords: haemophagocytic lymphocytosis; epstein barr virus; cytomegalovirus; cytokine storm; natural killer; macrophage; symptoms; cannabinoids

Abbreviations:

MCV= mean corpuscular volume, MCH= mean corpuscular hemoglobin, MCHC=mean corpuscular haemoglobin concentration, RDW= red cell distribution width, RBC= red blood cells, WBC= white blood cells, ANA= antinuclear antibody, CMV= cytomegalovirus, EBV= Epstein virus, Ig= immunoglobulins, Ab= antibody, DVT= deep venous thrombosis, DIC= disseminated intravascular coagulation, INR= international normalised ratio, PT= prothrombin time, PTT= partial thromboplastin time, aPTT= activated partial thromboplastin time, HR= heart rate, ABG= arterial blood gas, CPR=cardiopulmonary resuscitation.

Introduction

Hemophagocytic lymphocytosis (HLH) is a fatal autoimmune disease. It is a cytokine storm disorder characterized by a variety of inflammatory etiologies that result in excessive macrophage activation and uncontrolled hemophagocytosis, resulting in severe cytopenia [1]. These immune system disorders are reflected in the clinical presentation, which includes fever, liver and spleen enlargement, neurological abnormalities, hemodynamic instability, multi-organ failure, and death [2, 3]. The primary cause of HLH may be a genetic mutation, which is more prevalent in infants and young children and causes dysregulation of natural killer and T cell activity, resulting in the loss of normal feedback regulation of activated macrophages and excessive proliferous macrophages, or secondary to acquired triggers, such as infections like Epstein-Barr virus and cytomegalovirus, acquired immunodeficiency, hematological malignancies, particularly non-lympho Hodgkin's [3-5].

The cause of the patient's HLH in our case is still unknown since we are uncertain whether it was primary HLH or secondary HLH that had been activated by cannabis. In such a case, causal etiology may have redefined the cause of secondary HLH as primary HLH and vice versa, blurring the distinction between both subtypes. Our understanding of the pathophysiology in this case is still unclear, leading us to consider a number of theories. These theories contend that genetic, environmental, and social factors interact with one another to cause progressive inflammation that eventually reaches a critical point beyond which unchecked immune cell activation and excessive cytokine production result in the hallmark symptoms of HLH, resulting in the common end stage of fulminant HLH.

Since the disease is characterized by a prolonged fever of unknown origin as a presenting symptom that mimics infection, the majority of cases are misdiagnosed as sepsis at first [6]. The disease also manifests in nonspecific clinical pictures such as hepatosplenomegaly, lymphadenopathy, neurological complaints, involvement of other systems such as gastro intestinal, and respiratory systems [7,8,9], also symptoms due to complications, making a diagnosis difficult. Therefore, clinical lab findings such as a low level of NK cells (natural killer), neutropenia, thrombocytopenia, and an extreme elevation of ferritin, particularly in children rather than adults, are important in establishing the disease [10,11]. The presence of diseases that mimic the same clinical picture and presentation, such as Kawasaki disease or other autoimmune diseases, makes the search for the true diagnosis so exhaustive and difficult [12].

Five of the eight criteria in the HLH 2004 diagnostic protocol, are used to make the diagnosis. The clinical sign of HLH is hemophagocytosis, but this is not always the case in secondary instances, nor is it a criterion for a diagnosis [3,13]. The rarity of the disease and the existence of multiple differential diagnoses are the main causes of the delay in diagnosis, which has a negative impact on the prognosis [14]. Induction therapy for primary HLH includes dexamethasone and etoposide, followed by allogeneic bone marrow transplantation (the only cure option), whereas secondary HLH treatment varies depending on the causative trigger, but all patients receive steroids [2].

Case Presentation

We present a case of a 28-year-old male patient who was admitted to the hospital on November 21, 2022, with a history of high grade fever (42 °C) for two weeks, right lower limb swelling for three weeks, and right side weakness for one month prior to admission. The patient had no prior medical history except for a three-year cannabis addiction and a 15-year smoking habit. He also had no surgical or family history. Upon admission, the patient was alert, conscious, oriented, and vitally stable, according to physical examination. There was pallor, but no jaundice or cyanosis. There were significant palpable lymph nodes in the right submandibular and left axillary regions. The abdomen was lax and non-tender, with palpable hepatomegaly and an enlarged spleen 2 cm below the costal margin, but no ascites, and there was right lower limb edema. The chest was clear, with bilateral equal air entry. An electromyogram was performed prior to his admission for complaints of right foot paresthesia and right hand weakness; the findings were encouraging for severe right ulnar nerve demyelination associated with complete conduction block below the elbow, as well as severe right lateral popliteal nerve demyelination and severe axonal degeneration of the right sural nerve.

On admission, a complete blood count was performed, and the results were hemoglobin of 11.1 g/dl, hematocrit of 31.8%, MCV of 81.3 fl, MCH of 28.4 pg, MCHC of 34.9 g/dl, RDW of 15.6%, RBCs of 3.91 ul, platelets of 77 ul, WBCs of 1.90 ul, ANC of 1.150 ul, and C reactive protein of 54.7 mg/dl. Virology tests for HCV, HBV, and HIV were negative, the liver and renal function were also normal with no electrolyte abnormalities. Additionally, the blood, urine, and sputum cultures all came back negative. Urine analysis was also normal. Following this, the patient underwent Doppler examination of his bilateral lower limbs, which revealed right recent deep venous thrombosis, as well as ultrasound examination of his Neck, Axillary region, Abdomen, and pelvis, the results of which were favorable for multiple enlarged lymph nodes with Hepatosplenomegaly, followed by a whole body CT scan, which confirmed Hepatosplenomegaly (17 cm), well defined enhancing left adrenal soft tissue mass measuring 2.3 The echo study was unremarkable.

During this follow-up, the patient was given empirical antibiotics, but the high grade fever persisted, hence antibiotics were upgraded, targocid 400mg was added after 2 weeks of admission, after which the fever became of low grade type but persisted, so vfend, tinam, and colistin with dexa ampoules was added after 17 days of admission, and the patient received arkistra 2.5mg for DVT.

In order to determine the cause, a complete blood count film was performed, which revealed normocytic normochromic anemia, thrombocytopenia, and leucopenia. LDH was 2.163, Beta 2 microglobulin was 16.1mg/dl, serum protein electrophoresis was negative, and procalcitonin (PCT) was.9ng/ml. After we discovered the left adrenal mass by accident, we performed a Renin aldosterone ratio to rule out any endocrine problems, and it was normal at 1.8. The patient's clinical condition rapidly deteriorated, his liver and renal function increased, as did c reactive protein and procalcitonin, while albumin was 2.9 and protein creatinine ratio was 2.4. A complete blood picture revealed serial hemoglobin and platelet drops, and the patient received 6 packed RBCs on 10-11-12-13-14-15th December. As a result, Acyclovir, Septrin, and Targocid were discontinued on 18th December due to significant platelet drop.

After 2 weeks of admission, a bone marrow biopsy revealed heamophagocytic lymphohistocytosis, and Dexamethasone ampoule per day was started on the 7th of December before the result. Following that, liver and renal functions began to improve, as did pancytopenia, C reactive

protein, and procalcitonin, which all decreased significantly. Following the diagnosis, we continued our search for the cause, and on 18 December 2022, the results revealed CMV IgM negative, CMV IgG positive, EBV IgM negative, EBV IgG positive, Leishmania Ab negative, Brucella IgG, IgM negative, Lupus anticoagulant: negative, Beta 2 glycoprotein: negative, C4 was normal. Anti-cardiolipin antibodies are negative, and serum ferritin levels are 23456 ng/ml.

During the patient's hospitalization on 13 December 2022, he experienced a sudden attack of dyspnea in which his saturation dropped to 88% (Blood Pressure: 130/70, random blood sugar: 145, heart rate: 111 beats per minute, Temperature:37°C). A CT chest was performed, which revealed an intra-alveolar hemorrhage. Anticoagulant was stopped, Ethamylate and tranexamic acid were added, and pulse steroids 500mg were started for 5 days before starting Dexamethasone amp / 8h. After an attack of epistaxis, an ENT examination recommended CT with IV contrast of the nasal and paranasal sinuses, which revealed non-invasive fungal sinusitis. Because the patient was not fit for surgery due to thrombocytopenia, Amphotericin-B was recommended and started on 18 December 2022 along with saline nasal wash. Aside from DVT, the patient developed DIC; his INR was 1.14, (PT, PTT> 100 sec), Control time (PT) of 10.8 sec, APTT > 190 sec, PTT of 30.2 sec, and D-dimer of 17140 µg/L, indicating that cyclosporine was added on 21 December 2022. On 22 December, sudden desaturation of 82% caused a syncopal attack, for which ICU consultation was recommended. CT chest revealed right lobar pneumonia, bilateral pulmonary effusion, congestion treated with Furosemide 40mg twice daily, Nebulizers /8hours while CT brain and Urgent echo study were unremarkable (Blood pressure 120/80, random blood sugar 149 mg/dL, HR 120 beat per minute, temperature 36 °C, ABG: pH 7.51, pCO2 26, HCO3- 20.7). Following that, liver enzymes began to double or triple while biliary assessments were normal, so amphotericin B and cyclosporine were discontinued on December 25th, and pancytopenia worsened. On December 26, 2022, he received packed RBCs and a platelet transfusion on 23 and 25 December 2022. On December 26, 2022, after 36 days of admission, the patient died as a result of a syncopal attack (hypotension, tachycardia, and hypoxia were recorded, temperature was 36.5°C, ABG: pH 7.25, pCO2 23, HCO3- 10.1, lactate 12.5). Glucose 10%, 500 normal salines, a double dose of noradrenaline, Na bicarbonate ampoules were administered in conjunction with an oxygen mask and ABG monitoring (pH 7.30, p CO2 31, HCO3- 19, lactate 13). The patient's condition deteriorated faster than any test that could be performed, including neither a CT scan of the brain nor the chest. Instead, intubation with an ambo bag was performed when the patient was in a persistent shock state with CPR for 30 minutes on pulseless electrical activity.

Table 1.

Days after admission	RBCs x10^6	Hb g/dl	Hct %	PLT x10^3	WBCs x10^3
11/22/2022	L 3.91	L 11.1	L 31.8	L 77	L 1.9
11/23/2022	L 3.91	L 11	L 31.5	L 69	L 1.54
11/25/2022	L 3.72	L 11	L 31.3	L 60	L 1.5
11/27/2022	L 3.56	L 10.2	L 28.3	L 77	L 2.11
11/28/2022	L 3.26	L 9.2	L 26.3	L 71	L 3.26
11/29/2022	L 3.47	L 9.8	L 27.8	L 68	L 1.26
11/30/2022	L 3.09	L 9.1	L 25.4	L 71	L 1.57
12/1/2022	L 3.06	L 8.7	L 25.1	L 61	L 1.57
12/2/2022	L 3.19	L 8.6	L 25.8	L 69	L 1.34
12/3/2022	L 2.94	L 8.7	L 23.5	L 60	L 1.55
12/4/2022	L 2.94	L 8.0	L 23.7	L 80	L 1.51
12/5/2022	L 2.31	L 6.6	L 18.9	L 104	L 1.55
12/7/2022	L 2.38	L 6.3	L 19.8	L 145	L 1.5
12/8/2022	L 2.42	L 7.1	L 20.2	L 112	L 1.19
12/9/2022	L 2.51	L 7.00	L 21.6	L 113	L 2.6
12/10/2022	L 2.57	L 7.7	L 21.8	L 77	L 2.27
12/11/2022	L 2.79	L 8.1	L 23.7	L 43	L 2.63
12/12/2022	L 3.16	L 9.4	L 26.3	L 34	L 3.09
12/13/2022	L 3.19	L 9.6	L 27.4	L 27	L 2.49
12/14/2022	L 2.9	L 8.5	L 24.7	L 40	L 21.9
12/15/2022	L 2.95	L 8.8	L 25.7	L 44	L 2.22
12/16/2022	L 3.12	L 9.5	L 27.0	L 25	L 1.88
12/17/2022	L 2.98	L 9.1	L 25.7	L 18	L 1.52
12/18/2022	L 3.19	L 10	L 27	L 12	L 1.85
12/19/2022	L 3.15	L 10.3	L 26.6	L 15	L 2.23
12/21/2022	L 2.51	L 7.3	L 21.6	L 11	L 3.53
12/22/2022	L 1.87	L 5.6	L 16.2	L 10	L 2.71
12/5/2022	**complete blood picture film with Reticulocytes count**				
Normochromic normocytic anemia with aniso/poikilocytosis. White cells show marked leucopenia with absolute neutropenia and lymphopenia. Thrombocytopenia Reteculocytes Count 0.2%					
12/6/2022	**Bone Marrow Aspirate**				
Site: right posterior iliac crest. Differential count: blasts 1%, promyelocytes 3%, myelcytes (basophilic 0, eosinophilic 2, neutrophilic 11), metamyelocyte 10, basophilis 0, esinophilis 2, neutrophilis unsegmented 12, neutrophils segmented 15, lymphocytes 12, monocytes 2, erythroblasts 25, plasma cells 5 M/E ratio 2.2/1, Prussian blue stain increases macrophage iron stores.					

comment: hypercellular bone marrow, the megakaryocytes are increased in number, showing many giant sizes, granulocytic hyperplasia, erythroid hyperplasia with macro-normoblastic maturation, increased plasma cells, increased tissue histcytes showing evident hemophagocytosis

Table 1: presents complete blood picture and film also Bone Marrow Aspirate of the patient.

Table 2

Days after admission	CRP mg/L	Procalcitonin
11/22/2022	H 34.7 mg/L	NA
11/25/2022	H 27.7	NA
11/27/2022	H 87.3 mg/L	NA
11/30/2022	H 36 mg/L	NA
12/3/2022	H 53.4 mg/L	0.9 H
12/5/2022	H 86 mg/ L	NA
12/8/2022	NA	1.7 H
12/9/2022	H 16.4 mg/ L	NA
12/13/2022	NA	6.2 H
12/16/2022	H 27.6 mg/dl	NA
12/18/2022	H 53.7 mg/dl	1.5 H
12/21/2022	H 31.8 mg/l	NA

Table 2 presents Informatory Markers.

Table 3

Days after admission	Total bilirubin mg/dl	Direct bilirubin mg/dl	Serum albumin g/dl	Serum Creatinine mg/dl	ALT U/L	AST U/L	LDH U/L
11/22/2022	H 1.7 mg/dl	NA	L 3.2	N 0.7	H 150	H 167	H 325 U/L
11/23/2022	NA	NA	NA	N 0.7	NA	NA	NA
11/25/2022	H 1.7 mg/dl	NA	L 2.9 g/dl	N 0.8	H 209 U/L	H 176 U/L	NA
11/27/2022	H 6.4 mg/dl	NA	NA	NA	H 233 U/L	H 320 U/L	NA
11/29/2022	NA	NA	L 2.7g/dl	H 3.7 mg/dl	H 160 U/L	H 199 U/L	NA
11/30/2022	H 3.1 mg/dl	H 2.4	NA	H 3.2 mg/dl	NA	NA	H 2163 U/L
12/1/2022	NA	NA	NA	H 3.6 mg/dl	NA	NA	NA
12/2/2022	H 2.5 mg/dl	H 1.8	NA	H 3.3 mg/dl	H 112 U/L	H 166 U/L	NA
12/3/2022	H 2.8 mg/dl	H 2.0	NA	H 2.8 mg/dl	NA	NA	NA
12/5/2022	NA	NA	NA	NA	H 108 U/L	H 310 U/L	NA
12/7/2022	NA	NA	NA	H 3.1 mg/dl	H 80 U/L	H 189 U/L	NA
12/8/2022	NA	NA	L 3 g/dl	H 2.3 mg/dl	NA	NA	NA
12/9/2022	H 2.7 mg/dl	NA	NA	NA	NA	NA	NA
12/10/2022	H 3.9 mg/dl	NA	NA	H 1.5 mg/dl	H 215 U/L	H 67 U/L	NA
12/11/2022	H 4.3 mg/dl	H 3.3	NA	NA	NA	NA	NA
12/12/2022	NA	NA	L 3.2 g/dl	NA	NA	NA	H 3293 U/L
12/13/2022	NA	NA	L 3.0 g/dl	H 0.8 mg/dl	H 171 U/L	H 68 U/L	NA
12/14/2022	H 3.9 mg/dl	H 2.5	L 3.2 g/dl	NA	NA	NA	NA
12/15/2022	H 3.8 mg/dl	H 2.5	NA	NA	NA	NA	NA
12/16/2022	NA	NA	L 2.8 g/dl	H 0.7 mg/dl	H 162 U/L	H 72 U/L	NA
12/17/2022	NA	NA	NA	NA	H 124 U/L	H 264 U/L	NA
12/19/2022	NA	NA	NA	H 1.6 mg/dl	H 122 U/L	H 376 U/L	NA
12/20/2022	H 11.20 mg/dl	H 8.4 mg/dl	L 2.3 g/dl	NA	H 95 U/L	H 610 U/L	NA
12/22/2022	H 12.7 mg/dl	H 9.4 mg/dl	L 2.2 g/dl	NA	H 54 U/L	H 516 U/L	NA
Virology							
	HBs AG	**HBs AG**	**HIV**	**EBV IgG**	**EBV IgM**	**CMV IgG**	**CMV IgM**
11/22/2022	Non reactive	Non reactive	Non reactive	NA	NA	NA	NA
12/18/2022	NA	NA	NA	82 U/ml	4 U/ml	234 U/ml	0.2 U/ml

Table 3 presents chemistry and virology

Table 4

	11/27/2022	12/18/2022	11/26/2022	12/13/2022	12/18/2022
ANA	Negative	NA	NA	NA	NA

Anti-ds-DNA	Negative	NA	NA	NA	NA
ANCA-P	Negative	NA	NA	NA	NA
ANCA-C	Negative	NA	NA	NA	NA
Complement C4	NA	22.7 mg/dl	NA	NA	NA
Anticardiolepin IgG	NA	6.2 U/ml	NA	NA	NA
Anticardiolepin IgM	NA	3.8 U/ml	NA	NA	NA
Beta2 Glycoprotein IgG	NA	3.7 U/ml	NA	NA	NA
Beta2 Glycoprotein IgM	NA	2.1 U/ml	NA	NA	NA
Lupus anticoagulant	NA	1.04	NA	NA	NA
Beta 2 Microglobulin	NA	NA	H 16.1 mg/dl		NA
Renin	NA	NA	NA	121.1 pg/ml	NA
Aldosterone	NA	NA	NA	216.4 pg/ml	NA
Aldosterone Renin Ratio	NA	NA	NA	1.8	NA
Triglycerides	NA	NA	NA	NA	711 mg/dl
Ferritin	NA	NA	NA	NA	23456 ng/dl
Lashmania Ab	NA	NA	NA	NA	0.09 (Negative)
Brucella Abortus Ab	NA	NA	NA	NA	Negative
Brucella Melitensis Ab	NA	NA	NA	NA	Negative

Table 4 presents Immunology and other labs tests

Table 5

Date	Temperature °C	Blood transfusion (pack)	Platelets transfusion
21 November	42	NA	NA
22	41	NA	NA
23	40	NA	NA
24	40	NA	NA
25	40	NA	NA
26	38.5	NA	NA
27	38	NA	NA
28	40	NA	NA
29	38	NA	NA
30	40	NA	NA
1 December	40	NA	NA
2	39	NA	NA
3	38.5	NA	NA
4	40	NA	NA
5	38	NA	NA
6	39	NA	NA
7	38.5	NA	NA
8	38	NA	NA
9	37.5	NA	NA
10	38	**	NA
11	39	**	NA
12	37.5	**	NA
13	36.9	**	NA
14	37.8	**	NA
15	37	**	NA
16	38	NA	NA
17	37.3	NA	NA
18	37	NA	NA
19	38	NA	NA
20	38	NA	NA
21	36.9	NA	NA
22	37.7	NA	NA
23	38	NA	** 24 unit
24	37	NA	NA
25	37.9	NA	** 24 unit
26	37	**	NA

Table 5 shows the temperature in relation to the days after admission, as well as the blood and platelet transfusions performed on those days

Table 6

Name of the drug	Dose	Frequency/day	From	To
Alphentirn tab	2 tabs	3	22-Nov	18-Dec
Daflon, tab	1 tab	2	22-Nov	18-Dec
Folic Acid, Tab	1 Tab	1	22-Nov	18-Dec
Milga, Tab	1 Tab	1	22-Nov	18-Dec
Tavanic, 500mg, bottle	1 bottle	1	22-Nov	29-Nov
Septrin, tab	1 tab	Each 48h	23-Nov	18- Dec
Diflucan, 200mg, tab	1 tab	1	23-Nov	3-Dec
Acyclovir, 400mg, tab	1 tab	2	23-Nov	18-Dec
Arixtra, 7.5mg	1 amp	1	24-Nov	5-Dec
tazocin 4.5 gm vial	1 vial	4	24-Nov	30-Nov
Antodine, 20mg, Amp	1 amp	2	28-Nov	5-Dec
Amikin, 500mg, Vial	1 vial	1	29-Nov	3-Dec
Meronem, 2g, vial	1 vial	2	30-Nov	7-Dec
Targocid, 400mg, vial	1 vial	2	3-Dec	4-Dec
Targocid, 400mg, vial	1 vial	1	4-Dec	5-Dec
Contoroloc, 40mg, vial	1 vial	2	6-Dec	17-Dec
Danset, 8mg, amp	1 amp	2	6-Dec	12-Dec
fondaparinux sodium, 7.5mg	1 intradermal	1	6-Dec	5- Dec
Diflucan, 200mg, tab	1 tab	1	6-Dec	7-Dec
Targocid, 400mg, vial	1 vial	2	6-Dec	7-Dec
Colistin, 4.5 million IU, vial	1 vial	2	7-Dec	12-Dec
Tinam, 500mg, vial	1 vial	4	7-Dec	NA
Vfed, 200mg, tab	1 tab	2	7-Dec	NA
Dexamethasone, Amp	1 amp	2	7-Dec	21-Dec
Albumin, Bottle	1 bottle	1	7-Dec	26-Dec
Solu Medrol 500mg, vial	1vial	1	13-Dec	17-Dec
Gastreg, Amp	1 amp	3	17-Dec	18-Dec
potassium, amp	5 amp	2	17-Dec	18-Dec
Mucosta, Tab	1 Tab	3	17-Dec	26-Dec
Colistin, 4.5 million IU, vial	1 vial	2	17-Dec	NA
Targocid, 400mg, vial	1 vial	1	17-Dec	18-12
Antodine, 20mg, Amp	1 amp	2	18-Dec	26- Dec
Dexamethasone, Amp	1 amp	3	18-Dec	20-Dec
Ambizome 5 vial	1 vial	2	18-Dec	25-Dec
Dicynon, amp	2 amp	2	18-Dec	26-Dec
500ml ringer	500 mL	12	18-Dec	NA
potassium, 15mg, syrup	Syrup	3	19-Dec	NA
potassium, amp	3 amp	2	20-Dec	NA
Neoral, 50mg	1 amp	3	21-Dec	25-Dec
Calcium, amp	3 amp	2	NA	20-Dec

Table 6 presents the names and daily dosages of the medications administered throughout the patient's stay between the months of November and December

Legend

n=normal, H= high, L=low, RBCs= red blood cells, Hb=hemoglobin, Hct= hematocrit, PLT=platelets, WBCs= white blood cells, CRP=Creactive protein, NA= not available. Procalcitonin: Normal Range <0.5, Sever Infection >2 ALT= Alanine transaminase, AST= Aspartate transferase, LDH= Lactate dehydrogenase

HBsAg= Hepatitis B surface antigen, HCV Ab= Hepatitis C antibody, HIV=human immunodeficiency virus. EBV= Epstein Barr virus, CMV=Cytomegalovirus. EBV IgG: Negative <10 U/ml, Equivocal 10 -15 U/ml, Positive >15 U/ml. EBV IgM: Negative <9 U/ml, Equivocal 9-13 U/ml, Positive >13 U/ml. CMV IgG: Negative <0.5 U/ml, Equivocal 0.5 -1 U/ml, Positive >1 U/ml. CMV IgM: Negative <0.7 U/ml, Equivocal 0.7-1 U/ml, Positive >1 U/ml.

ANA= antinuclear antibodies, Anti-ds-DNA=anti-double stranded DNA, ANCA-P= Perinuclear anti-neutrophil cytoplasmic antibodies, ANAC-C= Anti-neutrophil cytoplasmic antibodies.

Complement C4 Normal range = (10-40) mg/dl

Lupus anticoagulant, Negative (0.8-1.2) U/ml, Weakly Positive (1.2-1.5) U/ml, Moderately Positive (1.5-2.0) U/ml, Strongly Positive >2.0 U/ml

Anticardiolepin IgG Normal range (Up to 10) U/ml

Anticardiolepin IgM Normal range (Up to 7) U/ml

Beta2 Glycoprotein IgG Negative <5 U/ml, Equivocal (5 -8) U/ml, Positive >8 U/ml.

Beta2 Glycoprotein IgM Negative <5 U/ml, Equivocal (5 -8) U/ml, Positive >8 U/ml.

M/E Ratio: The ratio of Maturing Myeloid cells to erythroid cells in the bone marrow.

*** (presence), NA: not available.**

amp= ampule, NA: not administrated.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder caused by abnormal histiocyte proliferation**.** It can be primary (Familial hemophagocytic lymphohistiocytosis), an autosomal recessive condition that typically manifests within the first year of life and is fatal if left untreated, or it can be found in a variety of genetic immunodeficiency diseases like X-linked lymphoproliferative syndrome (XLP), [15] or secondarily related to an infection such CMV, EBV, HSV, Rubella and Enterovirus, HHV-6, scrub typhus, or cancer [16-18].

HLH is frequently caused by infections, which are in turn caused by viruses (virus-associated hemophagocytic syndrome, VAHS) [19], most commonly in conjunction with herpes group viruses, specifically EBV. Cytomegalovirus, herpes simplex virus, adenovirus, parvovirus, echovirus, influenza virus, measles, and human immunodeficiency virus are among the other viruses involved in the development of VAHS. Only a few cases of VAHS caused by Rubella virus infection have been reported. Dual infections with the rubella virus and varicella zoster virus have also been reported [20], as has a case of Candida albicans and reactivated EBV infections [21], or from bacteria such as mycobacteria, mycoplasma, rickettsia, and murine typhus, particularly in patients returning from endemic or other tropical regions [18,22], Chlamydia pneumonia [23], and Capnocytophaga canimorsus bacteremia [21]. Protozoa and fungi are two additional infectious agents [13]. Malignant diseases are frequently seen in malignant lymphoma [20], which oncologists believe is a good imitator of HLH and can cause HLH diseases [24], though a case report of melanoma has also been identified [7]. Other important etiological factors that are considered rare but play an important role in the etiology of this disease are surgery, specifically silicone implants surgery for breast augmentation and reconstruction [3], which were found to be associated with anaplastic large cell lymphoma, despite being extremely rare but continuing to be reported [25, 26], proving that tumorogenesis and tumor progression have been linked to inflammation activating the pro inflammatory mediators as well as infections that are considered to be the key role for the activation of B and T cells [26]. Systemic lupus erythematosus and adult-onset still's disease, which represent a slightly different condition known as macrophage activation syndrome or MAS [22], as well as four genes (PRF1, UNC13D, STX11, and STXBP2), which all encode proteins necessary for lymphocyte cytotoxicity, have so far been found to have disease-causing mutations in primary HLH, which is passed down in an autosomal recessive manner. [2,20,27].

The primary **mechanism** of HLH is immune dysregulation, which results in altered natural killer cell and cytotoxic T-lymphocyte functions, increased macrophage activity, and, as a result, a cytokine storm. Among the cytokines that contribute to cytokine storms are interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-2, IL-6, IL-10, IL12, and IL16 [2, 28]. The cytokine storm is responsible for the laboratory findings and clinical manifestations of multiorgan damage seen in HPS. IL-6, IL-1, and TNF cause fever, whereas interferon and TNF cause hypertriglyceridemia by inhibiting lipoprotein lipase and promoting triglyceride synthesis. These cytokines also inhibit normal hematopoiesis, resulting in cytopenia [2, 13, 28]. Although the precise mechanism of secondary HLH is unknown, it is thought that tumor cells secrete cytokines and activate cytotoxic T cells. EBV appears to be involved in T cell activation, causing them to release proinflammatory cytokines such as TNF- and activate macrophages [2].

However, several **theories** about the etiological factors and pathogenesis were discussed while studying and interpreting this case. Did this patient have asymptomatic HLH that was triggered by EBV and CMV and become symptomatic a few weeks before his admission? Can Cannabis be a trigger for HLH? Has the reactivation of EBV been triggered by HLH, or has HLH been induced by the reactivation of EBV? Returning to our case report, we discovered that CMV IgG and EBV IgG were both positive, indicating a chronic infection [29], implying that the patient had previously been infected with these viruses. In this case, we can either stick to the epidemiological evidence and the causative role of EBV and CMV in HLH as described in the review and adopt the ***viral etiology theory.***

Also we can dig deeper in our case to find more epidemiological evidence regarding the causative factors for HLH. However, if we accept the first hypothesis, we must address whether HLH can be asymptomatic and for how long. If we follow the case order and what we have learned throughout our medical studies, IgG in EBV is positive means that the patient had the infection for more than 6 months, whereas IgG in CMV is positive means that he was infected with CMV at some point in their life but does not indicate when a person was infected.

In our case, the patient was undoubtedly infected with both viruses, but we don't know when. Patients with a genetic basis for HLH can sometimes remain asymptomatic until adolescence or even adulthood, according to research [30], and mutations in the six HLH-related genes (PFR, UNC13D, STX11, STXBP2, SH2D1A, and BIRC4) [31] cause decreased or absent perforin protein expression on the surface of cytotoxic cells [31]. Mutations that cause slight decreases in perforin expression and NK cell function may be the basis of HLH that is dormant until activated by external factors such as infection [32]. Viral infection, particularly EBV infection, is a major risk factor for HLH. Individuals with immune deficiencies such as X-linked lymphoproliferative syndrome (XLP) are usually asymptomatic prior to EBV infection, according to studies, and there is no clear genotype/phenotype correlation [33]. Because of differences in exposure, the onset and severity of HLH disease may vary

between individuals. In the absence of such triggers, the disease gene carrier may not exhibit any clinical symptoms.

This medical fact lends support to the theory that the patient had familial HLH because his medical history was not confirmed and his symptoms were not obvious until he became infected with these two viruses at the same time and his symptoms began to appear progressively and became aggressive.

Cannabinoids theory which were used by our patient for three years. Cannabinoids have been shown to influence the production and function of acute phase and immune cytokines, as well as the activity of network cells like macrophages and T helper cells, Th1 and Th2. These findings are significant because they demonstrate that cannabis can be immunomodulatory and, in certain circumstances, accelerate disease progression via apoptosis [34]. Defective apoptosis increases the production of pro-inflammatory cytokines, triggering a chain of events that leads to multiorgan failure and death. However, more research is needed to determine the health risks of cannabis consumption, as well as the role of the cannabinoid receptor ligand system in immune modulation and homeostasis, as well as in triggering HLH.

When the EBV EA IgG marker is elevated above normal levels, as it was in our patient, this may indicate that our patient reactivated a previous EBV infection. Infections and the development of HLH are well known to be linked. Viral, bacterial, fungal, or parasitic infections are all possible [35]. This suggests that, despite having a positive EBNA, our patient reactivated a previous EBV infection. EBV-HLH is a rare condition, but its prevalence is likely understated due to a lack of awareness of the diagnostic criteria and the similarity of its initial clinical presentation to a wide range of inflammatory and other infectious disorders. Furthermore, the presence of neutralizing antibodies does not rule out the possibility of EBV reactivation with subsequent EBV-HLH in an otherwise immune-competent individual.

This question with an answer means that EBV could have induced HLH or HLH could have reactivated a previous infection, ***HLH vicious cycle theory,*** and in both cases, this hypothesis cannot be rejected.

When writing this case, several questions were brought up. Since we lacked a satisfactory response regarding the pathophysiology, we thought about applying critical thinking to resolve the problem. Since these theories are connected and appear to follow a chronological order, we cannot reject them and instead must acknowledge them altogether.

Regarding the **clinical signs and symptoms** of HLH, individuals often exhibit nonspecific signs and symptoms, which makes a diagnosis difficult [36]. Adult patients are most likely to experience fever, rash, hepatosplenomegaly, lymphadenopathy, arthralgia, and neurologic impairment. Sepsis-like symptoms, such as edema, shortness of breath, diarrhea, hemorrhage, and sepsis, can appear in patients with severe HLH [6, 37]. All body systems are impacted by the high amounts of cytokines involved in the pathogenesis of HLH; central nervous system symptoms may take the form of seizures, ataxia, hemiplegia, mental status abnormalities, or irritability and may be linked to a spinal fluid hyperproteinemia [38]. The patient has hepatosplenomegaly, hyperbilirubinemia, and hypoalbuminemia, all of which indicate that the liver has been impacted early [36]. Jaundice and rash (sometimes known as a maculopapular rash or a nonspecific rash) are two common skin symptoms [39, 40]. Up to 40% of patients have reported having respiratory involvement, which can involve infections or acute respiratory distress syndrome (ARDS) [22].

HLH is a potentially fatal disorder caused by abnormal histiocyte proliferation; it can run in families or be associated with infections such as CMV, EBV, HSV, Rubella and Enterovirus, HHV-6, scrub typhus, or cancer [17, 18, 41]. The familial type is an autosomal recessive disease that primarily affects young children and is linked to a deficient apoptosis-inducing mutation in the perforin gene (PRF1)[42]. Seizures, meningismus, and irritability are the most common symptoms in neonates, regardless of whether the disease is primary or secondary [43]. A case of familial HPS with subdural effusion was also reported. Long-term survivors have neurological sequels, with the majority having neurodevelopmental delay and epilepsy, particularly in those with abnormal CSF and neurological symptoms, increasing the risk of mortality [42, 44]. A case of HHV-6-induced acute encephalopathy with biphasic seizures and late reduced diffusion was reported, and hypercytokinemia of HPS was thought to play an important role in the pathogenesis of the encephalopathy [17]. Another case was reported with haemorrhagic necrosis in cerebral white and grey matter with varying degrees of meningeal infiltration [45].

Ophthalmological findings in patients with HLH manifesting with retinal haemorrhage, retinal detachment, uveitis, pigment epithelial detachment, macular and optic disc edema, purtscher-like retinopathy, and papilledema may be caused by haematological anomalies, including severe anemia and coagulation abnormalities [46].

The difference between childhood cancer survivors and those of HLH is that both groups are survivors of chronic life-threatening illnesses, but the mean score for the HLH group was significantly lower on the psychosocial scale but not on the physical scale when compared with the mean scale of the cancer group [47]. Childhood survivors of HLH are at risk of long-term cognitive and psychosocial difficulties, which become most apparent in school age.

The variable clinical presentations of HLH, including fever, sepsis, and malignancies, as well as non-specific biochemical signs, make diagnosis difficult. Adults have HLH differently than children because it is more frequently caused by secondary causes in the former and is usually genetic in the latter. Furthermore, in the case of HLH caused by a malignancy, certain hematological malignancies can cause fever, cytopenias, liver dysfunction, and splenomegaly unrelated to HLH. Diagnostic criteria must be revised urgently in order to improve the sensitivity of existing tools [48]. In the setting of severe infection, autoimmune disease, or neoplastic disease, it is difficult to distinguish whether the patient has actual HLH or HLH-like illness such as macrophage activation syndrome and atypical hemolytic uremic syndrome; thus, HLH may develop as a result of rapidly progressive disease.

Clinicians should be prompted to consider HLH in patients with refractory shock and worsening sepsis. HLH can be diagnosed without the presence of hemophagocytes in the bone marrow, as well as in extramedullary organs such as the liver and spleen [49].The diagnosis of HLH is difficult. Because of the disease's similarity to many other diseases, such as sepsis [50]. A different difficulty brought on by HLH is macrophage activation syndrome (MAS), an acquired form of HLH that manifests in autoimmune diseases. It is most frequently reported in patients with systemic juvenile idiopathic arthritis (sJIA), and less frequently in those with systemic lupus erythematosus (SLE), adult-onset Still's disease (AOSD), rheumatoid arthritis (RA), spondyloarthropathy, and vasculitis [3].

The **diagnosis** of HLH is based on physical symptoms, physical exam findings, and several lab tests. The physical criteria known to be fever greater than 38 degrees, although it is not specific because it is known to be a common manifestation of several immune and inflammatory responses of all aetiologies, including infection and malignancies [51, 52]. However, fever of unknown origin (FUO) or fever unresponsive to treatment of the presumed primary cause can raise concerns about HLH in

critically ill patients [53, 54]. Cytopenia, which affects two or more cell lines, can occur as a result of sepsis, other autoimmune diseases, or even bone marrow cancer [55, 56]. In HLH-2004, hypofibrinogenemia (150 mg/dl) and/or hypertriglyceridemia (> 265 mg/dL) were combined as a single criterion (the rationale for this grouping is unknown) (57, 58). Hypofibrinogenemia is most commonly caused by disseminated intravascular coagulation (DIC), but it can also occur as a result of extensive liver injury or hemodilution [59].

In 30-80% of adult secondary HLH cases, hypertriglyceridemia is present [60, 61]. In HLH, hypertriglyceridemia may be caused by macrophage activation (macrophages being central components of lipid metabolism). Adults with secondary HLH have splenomegaly in 70-80% of cases [62]. It is, however, a common feature of a variety of other pro-inflammatory syndromes. Splenomegaly is, without a doubt, a common feature of many hematologic malignancies, particularly lymphoid and myeloproliferative neoplasms [63]. Serum ferritin elevation is one of the most well-known features of HLH, and nearly all cases of adult secondary HLH exceed the HLH-2004 cutoff of > 500 ng/mL [63]. Under normal conditions, macrophages, which are a major storage pool for ferritin, may release their reserves upon sufficient activation, precipitating the hyperferritinemia seen in HLH [64]. Natural killer (NK) cells help to eliminate damaged, stressed, or infected host cells, including macrophages [65]. In HLH, NK cells may fail to eliminate activated macrophages, resulting in immune dysregulation and maladaptive intensification [65]. Early HLH diagnosis and treatment result in a better prognosis. As a result, for critically ill patients with fever, multi-organ failure, and cytopenia, we should consider the diagnosis of HLH and begin treatment as soon as possible [21]. Patients with liver failure and persistent fever should be screened for HLH as soon as possible. Based on dynamic changes in liver function, HLH usually occurs in the middle and late stages, even during liver failure recovery, so it can lag behind or develop during liver failure recovery [66].

The initial **treatment** should begin right away. Meanwhile, research into the underlying disorder should be conducted. The goal of the initial treatment for both primary and secondary HLH is to calm down the hyperactive immune system and correct the hypercytokinemia. The first-line treatment is usually corticosteroid (CS). Lymphoma-associated HLH should be ruled out before starting CS because it can complicate lymphoma diagnosis. It is preferable to use dexamethasone (DEX) at a dose of 10 mg/m2/day or methyl prednisolone (mPSL) pulse therapy (20-30 mg/kg/day, maximum 1 g/day, 3 consecutive days). Instead of DEX, dexamethasone palmitate, which is absorbed by macrophages in inflammatory sites, may be used. High-dose intravenous immunoglobulin (IVIG) at a dose of 1 g/kg is frequently used as the first line of treatment in cases of infection-associated HLH. Plasma exchange or exchange transfusion may be used to quickly eliminate the cytokines and enhance the coagulation state [67 ,68].

In the event of opportunistic infection, coagulopathy, hepatic damage, and renal failure, supportive care is also crucial. Trimethoprim-sulfamethoxazole (5 mg/kg/day as trimethoprim) and an antimycotic drug are advised for preventative use.

Fever is the primary marker of treatment response. It is imperative to switch quickly to the next therapeutic strategy if the fever lasts for more than 48 hours after the start of treatment [69].

Table 7

Diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled **1. A molecular diagnosis consistent with HLH** 2. **Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)**
Initial diagnostic criteria (to be evaluated in all patients with HLH) **Clinical criteria** ● Fever ● Splenomegaly **Laboratory criteria** ● Cytopenias (affecting > 2 of 3 lineages in the peripheral blood) Hemoglobin (< 90g/L), platelets (<100 x10^9/L), Neutrophilis (<1.0 x 10^9 /L) (In infants <4weeks: Hemoglobin < 100 g/L) ● Hypertriglyceridemia and/or hyperfibrinogenemia (fasting triglycerides ≥3.0 mmol/L (i.e ≥ 265mg/dL), fibrinogen ≤1.5 g/L) **Histopathologica criteria** ● Hemophagocyosis in bone marrow or spleen or lymph nodes. No evidence of malignancy **A. New diagnostic criteria** ● Low or absent NK-cells activity (according to local lab reference) ● Ferritin ≥500 microgram/L ● Soluble CD25 (i.e soluble IL-2 receptor) ≥2400 U/ml

Table 7 shows diagnostic guidelines for HLH-2004 (70)

Conclusion

HLH is a rare multi-organ progressive disorder that is probably underdiagnosed. It is a terrifying illness imitation. Although uncommon, the condition is typically assessed once the patient meets the majority of the diagnostic requirements, which may be after ruling out other possibilities late in the course. The mortality rate is consistently high, so early diagnosis is essential. It is crucial that we inform our coworkers about the disease's rising prevalence and the possibility that it may start as a typical case of prolonged fever. Due to the lack of specific signs and symptoms, the initial symptoms of HLH may be vague and deceptive. Patients who have a persistent high fever, splenomegaly, and cytopenias should be tested for HLH. As a result, a high level of suspicion, as well as a comprehensive clinical, immunological, and genetic workup, are required. The key to survival is to start appropriate therapy as soon as possible. Although there have been significant advances in medicine, overall survival rates are still low. We treated our patient empirically with

potent antibiotics, antifungals, and antiviral medications with no improvement despite cultures being negative and serology for CMV and EBV IGg only being positive, indicating past infection because it did not respond to antiviral medication, which is a common trigger in both genetic and acquired HLH. Infections are common causes of HLH, both genetic and acquired, and we thought this was the case in our patient.

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