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Unveiling the Enigma: A Case of Hodgkin's Lymphoma to Diffuse Large B-cell Lymphoma, Culminating in Hemophagocytic Lymphohistiocytosis

Sharanya Rajgopal[1]*, Hashwin Pilathodan[1], Yash Bhalala[1], Malvika Krishna[1], Amit K. Correa[1]

[1]*Hematology and Oncology, University of Texas Health, Memorial Hermann Cancer Center, Houston, USA*

***Corresponding author:** Sharanya Rajgopal, Hematology and Oncology, University of Texas Health, Memorial Hermann Cancer Center, Houston, USA.

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Abstract

Hemophagocytic lymph histiocytosis (HLH) is a rare complication that occurs after Hodgkin's lymphoma, with an estimated incidence of 8.9 %. This case highlights the complexities of diagnosing and managing Hemophagocytic Lymph histiocytosis (HLH), particularly when it arises as a complication of Hodgkin's Lymphoma (HL) that has progressed to T-cell/histiocyte-rich large B-cell lymphoma. A 36-year-old man with a history of Hodgkin's lymphoma presented with severe systemic symptoms and was diagnosed with Hemophagocytic lymph histiocytosis based on clinical criteria and laboratory findings. Despite aggressive treatment, including chemotherapy and antibiotics, the patient developed Tumor Lysis Syndrome (TLS), acute kidney injury (AKI), and multisystem organ failure, ultimately leading to his death. This case underscores the urgent need for early recognition and intervention in Hemophagocytic lymph histiocytosis, especially in the context of underlying malignancies, and highlights the challenges posed by its rarity and complex presentations. Prompt consultation with hematologists and immediate treatment initiation are critical to improving outcomes.

Categories: *Allergy/Immunology, Oncology, Hematology*

Keywords: Hypercytokinemia, Increased Ferritin, Uncontrolled Hyperinflammatory Reaction, Hemophagocytosis, T Cell Histiocyte Rich Large b Cell Lymphoma.

Introduction

Hemophagocytic lymphohistiocytosis [HLH] is a severe condition where cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages become excessively activated, leading to high levels of cytokines and immune-related damage to multiple organs. It is classified as either primary, caused by genetic mutations that disrupt important proteins needed for the proper functioning of cytotoxic T cells and NK cells, or secondary, which is caused by a malignant, infectious, or autoimmune stimulus without a known genetic cause [1].

Hemophagocytic lymphohistiocytosis related to Hodgkin's lymphoma was documented in 8.9% of the total cases. The age-standardized incidence rate for Diffuse Large B Cell lymphoma [DLBCL] was 7.2 per 100,000, according to data from the United States cancer registry. It is impossible to define the true incidence of Hemophagocytic lymphohistiocytosis because some people view it as a faith-based diagnosis. We admit that the "I know it when I see it" justification falls short of current diagnostic criteria in medicine [2-3].

Nonetheless, certain data indicate that this distinct clinical category of Hemophagocytic lymphohistiocytosis is defined by the level of inflammation as specified by the Hemophagocytic lymphohistiocytosis-2004 criteria. Moreover, the phenotype is more severe than that of the majority of other inflammatory conditions, and survival for patients diagnosed with Hemophagocytic lymphohistiocytosis was less than 10% before immune chemotherapeutic treatment strategies were developed. According to HLH-94, the 5-year overall survival was 54%, with 94% of

deaths in patients with uncontrolled disease occurring in the first eight weeks. These results imply that individuals classified as "Hemophagocytic lymphohistiocytosis" comprise a subset with severe pathologic inflammation requiring prompt immune suppression [4-5].

Thanks to the advances in our understanding of the genetic origins of inherited Hemophagocytic lymphohistiocytosis and the use of contemporary sequencing technology, every infant diagnosed in Sweden using the HLH-2004 criteria over a six-year study had Hemophagocytic lymphohistiocytosis-associated genetic variants identified. According to a larger series, 40-80% of people with Hemophagocytic lymphohistiocytosis finally have an inherited condition that has been confirmed to be genetic. The HLH- 2004 criteria, despite their imperfections, offer a certain level of specificity when it comes to selecting critically ill individuals who should be given special consideration for Hemophagocytic lymphohistiocytosis diagnosis and treatment [6-8].

How to cite this article

The incidence of primary Hemophagocytic lymphohistiocytosis in Sweden as estimated by the national registry was 1.5 cases per million live births in 2007-2011, compared to 1.2 cases per million in earlier studies (1987-1996; 1997-2006), owing to better sequencing technology and a better understanding of the genetic predisposition of the disease. In North America, race and ethnicity have a major impact on the prevalence of particular gene abnormalities. The incidence of Hemophagocytic lymphohistiocytosis in children and adults is likely influenced by genetic heterogeneity, the presence of founder mutations, ethnic background, and the frequency of Hemophagocytic lymphohistiocytosis associated triggers [9-10].

We believe that depending on the degree of suspicion and medical culture of specific institutions, screening for and consideration of Hemophagocytic lymphohistiocytosis also differs significantly. Either adult Hemophagocytic lymphohistiocytosis incidence is skyrocketing, or awareness of the condition is growing. A PubMed search for "adult" and "hemophagocytic lymphohistiocytosis" yielded 893 papers in 2000-2010, but 206 in 2015-2024. Hemophagocytic lymphohistiocytosis is often not detected on time due to non-specific symptoms and a delay in diagnosis. This leads to the rapid progression of Hemophagocytic lymphohistiocytosis and ultimately multi-organ failure.

We will be discussing a unique case of Hemophagocytic lymphohistiocytosis in which the patient was first diagnosed with Hodgkin's lymphoma, which then progressed to large B cell lymphoma, and then transformed into hemophagocytic lymphohistiocytosis [HLH].

Case Presentation

A 36-year-old man came with a history of recurrent nodular lymphocyte-predominant Hodgkin's lymphoma that later changed into T-cell/histiocyte-rich large B-cell lymphoma and Tuberculous lymphadenitis in the lymph nodes of his right axillary armpit.

The patient was diagnosed with Hodgkin’s lymphoma and treated elsewhere in the year 2000; he completed chemotherapy and was diagnosed with recurrent Hodgkin’s lymphoma in April 2018. Hodgkin’s lymphoma transformed into a T-cell/histiocyte-rich large B-cell lymphoma with hepatosplenic involvement, which was diagnosed in October 2023. He was diagnosed with Tuberculosis on his right axillary lymph node in June 2023.

The patient came to the hospital emergency department in February 2024 for malaise, decreased oral intake, vomiting, abnormal lab values of low bicarbonate, low sodium, and high potassium levels, renal failure with hyperuricemia, and hyperbilirubinemia. He presented with symptoms of fever, vomiting, diarrhea, abdominal pain, oliguria, and edema of the right upper extremity. He developed a cough, which was treated with guaifenesin. A CT chest was ordered, which revealed moderate right-sided pleural effusion and stable small left pleural effusion. (Figure 1).

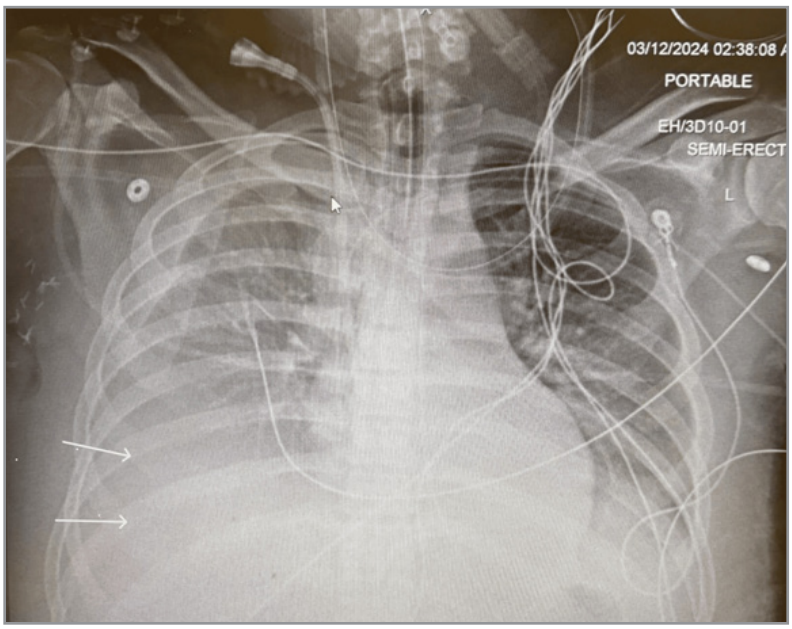

Figure 1: Portable chest X-ray in a semi erect position, AP view; (white arrows; showing increased opacity and blunting of R costophrenic angles), depicting moderate pleural effusion.
AP - anteroposterior. R-right.

On physical examination, the patient was febrile with marked hepatosplenomegaly, abdominal distention, bilateral edematous upper and lower extremities, and an icterus.

An ultrasonogram of the abdomen was done, which found hepatosplenomegaly with multiple hyperechoic lesions. A peripheral blood smear showed pancytopenia, necessitating a bone marrow biopsy, which revealed hemophagocytosis and no increase in blasts. Thrombocytopenia was seen as likely in the setting of hepatosplenomegaly and cancer involvement, (Figure 2).

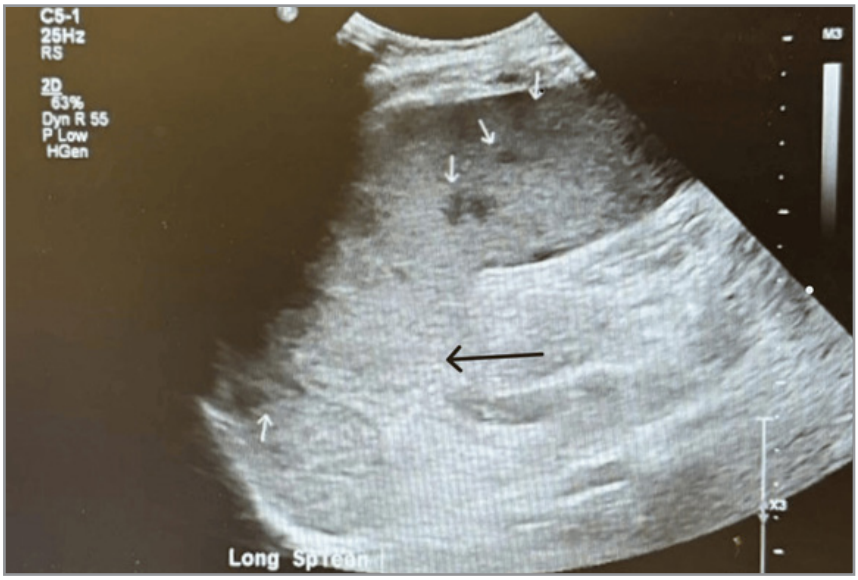

Figure 2: Ultrasound ABD depicting Splenomegaly, (Black arrow; splenomegaly, white arrow; hyperechoic lesions in the spleen) ABD - abdomen.

The patient met 7 out of the 8 diagnostic criteria for Hemophagocytic Lymphohistiocytosis (HLH) according to the HLH-2004 protocol, confirming the diagnosis. The criteria fulfilled include a persistent fever greater than 38.5°C, splenomegaly, decreased fibrinogen levels (81 mg/dl), elevated triglycerides (791 mg/dl), evidence of hemophagocytosis in a bone marrow biopsy, (figure 3), significantly increased ferritin levels (>7500 ng/ml), and pancytopenia. Additionally, the patient presented with lactic acidosis (11.4 mmol/l), indicating severe systemic illness, although this is not part of the HLH-2004 criteria. Given that only 5 out of 8 criteria are required for diagnosis, this combination of clinical and laboratory findings strongly supported the diagnosis of Hemophagocytic lymphohistiocytosis, necessitating urgent initiation of appropriate immunosuppressive therapy [11].

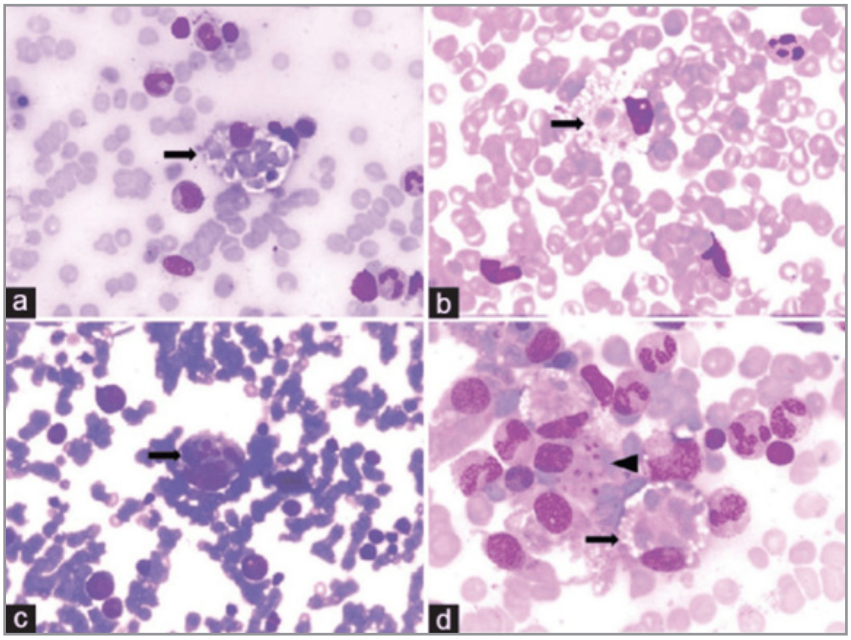

Figure 3: Bone marrow aspirate showing Hemophagocytosis , May –Grunwald Giemsa (MGG) Stain, ×400

(a) Arrow shows macrophage engulfing red blood cells (RBCs), (b) Arrow shows macrophage engulfing RBCs and platelets. (c) Arrow shows macrophage engulfing neutrophil. (d) Bone marrow aspirate, MGG Stain, ×1000. Arrow shows macrophage engulfing RBCs, arrowhead shows macrophage engulfing RBCs and platelets. Reproduced/adapted from Vandana et al., with permission from International Journal of Applied and Basic Medical Research.

Table 1: laboratory values
Hb: Hemoglobin, WBC: white blood cell, CRP: C-Reactive protein, ALT: alanine transaminase, AST: aspartate aminotransferase, ALP: alkaline phosphatase , FEU: Fibrinogen Equivalent Units.
The Relevant Laboratory Findings for the Patient are as Follows: (Table 1).

Test	Lab Values	Reference Range
Lactic acid	11.4 mmol/L	< 2 mmol/L
W.B.C	0.1 × 10^9/L	4.5 to 11 × 10^9/L
Platelets	80,000 × 10^9/L	150 to 400 × 10^9/L
Fibrinogen	81 mg/dL	190-503 mg/dL
D-dimer	3.58 mcg/mL FEU	0.27-0.48 mcg/mL FEU
Phosphorus	6.8 mg/dL	2.5-5.0 mg/dL
Hb	5.1 g/dL	14-18 g/dL
Triglyceride	791 mg/dL	< 150 mg/dL
CRP	20.5 mg/dL	< 10 mg/dL
Ferritin	> 7500 ng/dL	23.4-336.2 ng/dL
Bilirubin	10 mg/dL	0.2-1.2 mg/dL
ALP	198 U/L	34-104 U/L
AST	150 U/L	13-39 U/L
ALT	91 U/L	7-52 U/L
Direct bilirubin	6.8 mg/dL	0-0.2 mg/dL

Table 2: Medical timeline chronological order
LN : lymph node , AFB : acid fast bacilli, R- CHOP : Rituximab, Polatuzumab ,Cyclophosphamide, Doxorubicin, Prednisone.
The Medical Timeline Chronological Order is as Follows:(Table 2).

Date	Diagnosis
2000	Hodgkin's Lymphoma
April 2018	Nodular lymphocyte predominant Hodgkin's lymphoma in Right Axillary and inguinal lymph nodes
June 2023	Right Axillary LN Biopsy positive for AFB (granulomatous lymphadenitis)
October 25, 2023	T-cell /Histiocyte-rich Large B-cell Lymphoma
January 19, 2024	R-CHOP regimen initiated
March 5, 2024	Cyclophosphamide, Dexamethasone, Rituximab treatment initiated

The treatment protocol for Hemophagocytic lymphohistiocytosis for the patient was executed as follows: For the Tuberculous lymphadenitis, the patient was given therapy with the RIPE protocol (Rifampin, Isoniazid, Pyrazinamide, and Ethambutol) starting in December 2023.The patient was initially diagnosed with nodular lymphocyte-predominant Hodgkin's lymphoma in the right axillary and inguinal lymph nodes, which later transformed into T-cell histiocyte-rich large B-cell lymphoma.

The R CHOP regimen was started for thepatient, which consists of Rituximab, Polatuzumab, Cyclophosphamide, Doxorubicin, and Prednisone. This R-CHOP regimen was initiated on January 1, 2024.On March 3, 2024, the patient received hyperfractionated cyclophosphamide, 40 mg dexamethasone, and Rituximab. The regimen was as follows: Cyclophosphamide 300 mg/m2 i.v. on days 1, 2, and 3; Mesna 600 mg/m2 infusion for bladder protection on days 1, 2, and 3; Dexamethasone 40 mg PO on days 1, 2, and 3; and Rituximab 375 mg/m2 i.v. on day 4. The patient's bone marrow biopsy was positive for hemophagocytosis being present. The patient's H-score was 288.

The treatment regimen for Hemophagocytic lymphohistiocytosis was started, which consisted of 10 mg of Dexamethasone BID and i.v. immunoglobulin initially. Later on, treatment with Rituximab and 40 mg of dexamethasone was started. The patient developed a labile BP due to Rituximab, so the patient was started on cyclophosphamide, mesna, and 40 mg of dexamethasone by midnight on March 5, 2024. Filgrastim 480 mcg was administered to the patient daily. The patient developed a fever and bacteremia. Blood culture showed Klebsiella pneumonia, for which Vancomycin intermittent dosage and Meropenem 500 mg i.v. q6h were administered. The patient went on to develop Acute Kidney Injury, presumably from tumor lysis syndrome, requiring continuous renal replacement therapy, which was later discontinued and transitioned to hemodialysis due to improvements in tumor lysis syndrome. Etoposide was planned to be started, but the patient succumbed to multi-system organ failure.

Discussion

In the above case study, the intriguing factor is the transition of Hodgkin's lymphoma to large B-cell lymphoma, which then tran-

sitions again to hemophagocytic lymphohistiocytosis. The result of a severe, uncontrolled hyperinflammatory reaction, which is typically brought on by an infectious agent, is hemophagocytic lymphohistiocytosis (HLH). Chronic activation of lymphocytes and histiocytes causes hypercytokinemia, which in turn causes the symptoms that are specific to Hemophagocytic lymphohistiocytosis. Cytotoxic granules in natural killer cells and cytotoxic T lymphocytes are transported, processed, and function differently in cases of familial Hemophagocytic lymphohistiocytosis [HLH] and immunodeficiency disorders linked to albinism due to genetic abnormalities. This results in faulty target cell death and an ineffective immune response. Adults and teenagers are also increasingly being found to have the abnormalities. In addition to patients with iatrogenic immunosuppression, cancer patients, and autoinflammatory and autoimmune illnesses (macrophage activation syndrome), acquired Hemophagocytic lymphohistiocytosis can also arise in otherwise healthy individuals who are infected [12].

A potential diagnosis of hemophagocytic lymphohistiocytosis (HLH) can be indicated by either a molecular diagnosis consistent with Hemophagocytic lymphohistiocytosis, such as mutations in genes like PRF1, UNC13D, STX11, or RAB27A, or by meeting five out of the following eight clinical and laboratory criteria: a body temperature higher than 38.5 °C, hepatosplenomegaly, cytopenia affecting at least two out of three blood cell lines (with hemoglobin <9 g/dL, platelets <100×10⁹/L, and neutrophils <1.0×10⁹/L), hypofibrinogenemia and/or hypertriglyceridemia (with fasting triglycerides >3.0 mmol/L or fibrinogen ≤1.5 g/L), hemophagocytosis in tissues such as lymph nodes, liver, spleen, or bone marrow, minimal or absent NK cell activity, serum ferritin levels ≥500 µg/L, and soluble IL-2 receptor (sCD25) levels ≥2400 U/mL [13].

Let us now delve deeper into the immunological process behind hemophagocytic lymphohistiocytosis. The immune system uses natural killer [NK] cells and cytotoxic T lymphocytes (CTLs) to primarily fight infections brought on by intracellular pathogens through contact-dependent cytotoxicity. All of these lymphocytes, such as T-regulatory cells, Natural killer cells, and Cytotoxic T Lymphocytes, regulate inflammatory and infectious conditions in the immune system and other organs, and Hemophagocytic lymphohistiocytosis [HLH] can result from genetic abnormalities in these lymphocytes [14].

They contribute to the host's defense mechanism against cancer and primary and secondary viral infections. Natural killer cells directly target diseased or wounded cells since they are unaffected by the major histocompatibility complex (MHC) class I. Activated natural killer cells release cytotoxic granules and granzymes containing perforin at the synaptic junction between cytolytic cells (NK cells and CTLs) and their target cells. This causes the target cells to lyse through both caspase-dependent and caspase-independent apoptosis [15-17].

For this reason, it's critical to identify Natural killer cell depletion as soon as possible to start therapy and prevent potentially fatal consequences. Two different mechanisms can activate caspases: one is intrinsically mediated by the mitochondria, and the other is mediated by the extrinsic death receptor. The extrinsic pathway that is better understood is the one that is started by death receptor CD95 activation. Although the CD95 receptor's cytoplasmic domain lacks intrinsic function, it does include a death domain that can facilitate protein interactions. The adaptor protein FADD, also known as Mort1, is recruited when CD95 is activated by its ligand, CD95L, via the death domain [18-19].

After FADD is recruited, caspase-8 is also attracted to the receptor, whereupon autoproteolytic cleavage via oligomerization facilitates the receptor's activation. Apoptosis is the outcome of caspase-8 activating downstream effector caspases, namely caspase-3. The intrinsic apoptotic process entails caspase-9 activation and the release of cytochrome c, which are components of the mitochondria's apoptotic activity. The cytosolic apoptotic protease activating factor-1 (Apaf-1) and caspase-9 interact to produce the apoptosome, an apoptotically active complex that forms when dATP and cytochrome c are present. The apoptosome can then cleave caspase-3 after activating caspase-9 [20-24].

NK cells do not recognize target cells; T cells recognize target cells by binding specific MHC class I/peptide complexes on target cells with specialized T-cell receptors. Cytotoxic T lymphocytes destroy autologouscells that are associated with foreign antigens through MHC class I. Consequently, the immunosurveillance of intracellular homeostasis by Cytotoxic T lymphocytes is based on the presentation of MHC class I peptide. Conversely, protein shortages and ineffective antigen clearance in Hemophagocytic lymphohistiocytosis are caused by genetic diseases. This leads to a disruption of the host defense and immune surveillance systems. Another theory is that insufficient antigen clearance leads to improper hemophagocytosis and extended immunological activation, (figure 4) [25-28].

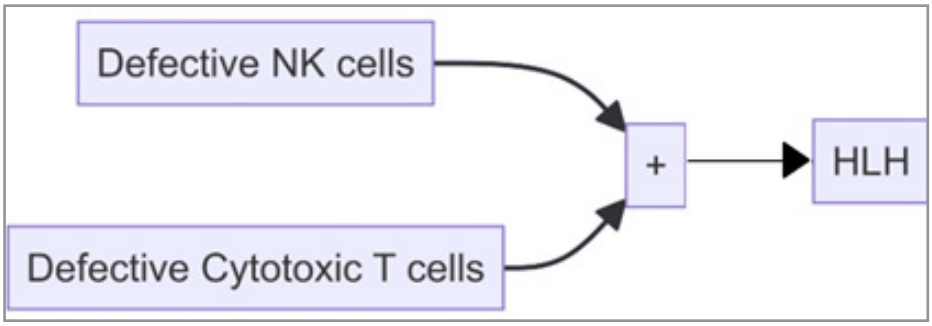

Figure 4: The pathophysiology of HLH is closely related to the compromised cytotoxicity offered by NK cells and CTLs. HLH stands for hemophagocytic lymphohistiocytosis; NK stands for natural killer; and CTL for cytotoxic T lymphocytes. Reproduced/adapted from Bseiso et al. with permission from Cureus.

Now, let's take a closer look at how the inflammatory pathway functions in the development of hemophagocytic lymphohistiocytosis. The primary indicators of Hemophagocytic lymphohistiocytosis, a multisystem hyperinflammatory disease, are T cells and macrophage hyperactivation. The disease's clinical symptoms are brought on by an excess of type 1 T-helper (Th1) cytokines, including interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF-α), and IL-2. Uncontrolled macrophage activity and dysfunctional T cells lead to tissue injury, immunological dysregulation, and increased cytokine production [29].

Th1 and Th2 cell balance is regulated by IL-12 and IL-4. B cells and macrophages both produce IL-12, which promotes the Th1 response and IFN-γ synthesis. Additionally, IFN-γ stimulates the production of IL-12, which directly increases the number of Th1 cells and aids in the differentiation of Th0 and Th1 cells. IL-4 is another significant Th2 cytokine that encourages the growth of Th2 cells. Th1 cells stimulated by IL-12 and Th2 cells induced by IL-4 both produce IL-10, which inhibits the production of IL-12 as well as other Th1 cytokines such as IFN-γ and IL-2, (figure 5). The inhibitory properties of IL-10 as an anti-inflammatory medication lower pro-inflammatory cytokine. As a result, IFN-γ, IL-10, 1L-4, and IL-12 are the primary cytokines implicated in Hemophagocytic lymphohistiocytosis [30].

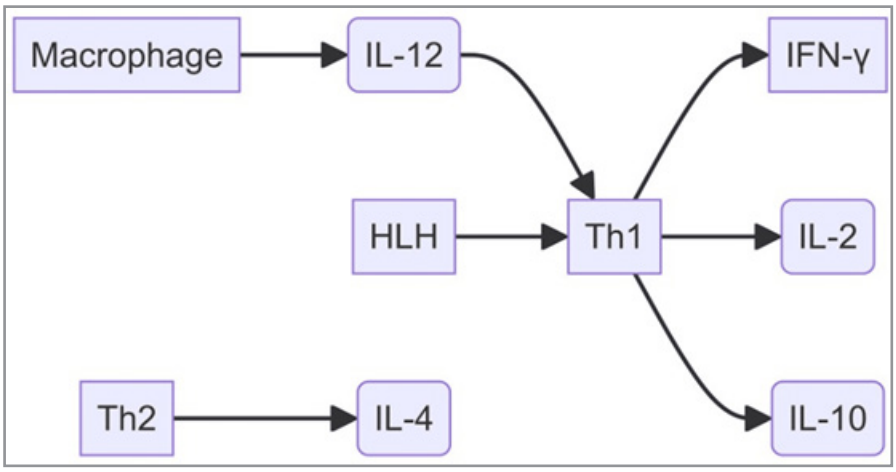

Figure 5: The production of IL-2, IL-4, IFN-γ, IL-10, and IL-12 is shown as a significant route in HLH by the Th1, Th2, and macrophage paradigm.
IL stands for interleukin; IFN-γ for interferon-gamma; HLH for hemophagocytic lymphohistiocytosis; Th1 and Th2 are types of T helper cells. Reproduced /adapted from Bseiso et al. with permission from Cureus.

Osugi et al. investigated 11 patients with Hemophagocytic lymphohistiocytosis to look at the synthesis of IL-10, which suppresses the Th1 response, and IL-12 and IL-4, which stimulate the Th1 and Th2 responses, respectively. The results showed that while all Hemophagocytic lymphohistiocytosis patients had elevated levels of IL-12 and IL-10, none of them had any measurable IL-4 levels. As a result, the research concluded that Th1 cells produce more cytokines than Th2 cells, which facilitates their faster development.

Additionally, both cell types demonstrated a significant role in the pathophysiology of Hemophagocytic lymphohistiocytosis. Nevertheless, the overproduction of IL-10 inhibited the diseased patients' hyperactive Th1 cells and monocytes/macrophages. Now, let's explore macrophage activation syndrome in more detail. Macrophages are typically the cells that expose lymphocytes to foreign antigens so that the latter can be eliminated directly by the lymphocytes or converted into antibodies. Macrophages become activated and release cytokines in different kinds of Hemophagocytic lymphohistiocytosis. In turn, if cytokines are released in excess, they may harm organs [31-32].

The pathophysiology of secondary Hemophagocytic lymphohistiocytosis involves Macrophage activation syndrome as a deadly underlying mechanism. The excessive production of cytokines, or "cytokine storm," is caused by macrophage overstimulation. Rheumatic illnesses like systemic juvenile idiopathic arthritis and systemic lupus erythematosus can be the cause of it [33-36]. Macrophages assist lymphocytes in producing antibodies against foreign antigens or directly destroying them as antigen-presenting cells. An oversupply of cytokines is released by activated macrophages during Hemophagocytic lymphohistiocytosis, leading to severe tissue damage and multisystem organ failure [37-38].

The significant cytokine production that permeates all tissues and results in necrosis and organ failure controls these manifestations. Macrophage activation syndrome should be closely monitored in individuals with Hemophagocytic lymphohistiocytosis since it can manifest in patients with autoimmune and autoinflammatory illnesses [39-40].

Treatment of HLH

Hemophagocytic lymphohistiocytosis has a potentially fatal pathology. Patients with hereditary Hemophagocytic lymphohistiocytosis have a short survival time if treatment is not received. The majority of treatment development has taken place in pediatric facilities, where Familial lymphohistiocytosis [FLH] is the primary cause of Hemophagocytic lymphohistiocytosis. Nevertheless, unless there is another child in the family who has Hemophagocytic lymphohistiocytosis, it is frequently challenging to differentiate between secondary and familial Hemophagocytic lymphohistiocytosis at presentation. Therefore, whether or not Hemophagocytic lymphohistiocytosis is secondary or inherited, severe Hemophagocytic lymphohistiocytosis can be treated with HLH-specific therapy.

Given that cytokine overproduction in Hemophagocytic lymphohistiocytosis can result in hemodynamicinstability and multiorgan damage and that the condition is frequently brought on by infections or cancers, a three-pronged approach to treatment is necessary.1. Patient stabilization and organ support.2. Look for triggers, such as infections or cancer, and try to control them.3. Suppression of an excessive inflammatory response: Since pathophysiologic evidence indicated that T cell-dependent immunological dysregulation predominated, T cell-dependent immune control has recently become the main focus of treatment [41].

The Histiocyte Society created the first worldwide treatment plan for Hemophagocytic lymphohistiocytosis in 1994, which led to a significant rise in survival to 55% with a median follow-up of 3.1 years. Even though the HLH 94 regimen had a noticeably better outcome, early death remained an issue. To address the issues with the HLH-94 protocol, the HLH-2004 protocol was created in 2004. It was based on the HLH 94 protocol with a few adjustments. Owing to HLH 94's significant early death rate during the hematopoietic cell transplantation (HCT) phase, cyclosporine A (CSA) was administered during the induction treatment to intensify the initial course of treatment. A minority of patients were advised to have intrathecal methotrexate (MTX) in addition to corticosteroids (prednisolone). When HLH 2004 was compared to HLH 94, there was a significant reduction in pre-HCT mortality from 27 to 19% and a shorter period from treatment initiation to Hematopoietic cell transplantation.
Anti-thymocyte globulin was used in place ofetoposide in different single-center research studies, which revealed similar survival rates with less toxicity but a higher rate of relapse [42].

HLH 94 Treatment Protocol
Introductory treatment (induction therapy): For critically ill patients, etoposides and corticosteroids must be administered promptly to stop the inflammatory process linked to Hemophagocytic lymphohistiocytosis, except for Macrophage activation syndrome and malignancy-associated Hemophagocytic lymphohistiocytosis.Etoposide (150 mg/m2 twice weekly for two weeks, and then weekly) and dexamethasone (10 mg/m2 initially, then 5 mg/m2, 2.5 mg/m2, 1.25 mg/m2, and one week of tapering) are the induction therapies for the HLH-94 regimen.

Patients should be closely watched during induction therapy to watch for potential problems as well as signs of improvement. When a patient responds well to the first course of treatment, their symptoms go away, and their lab results return to normal. However, patients who do not react to treatment within two to three weeks of the initiation of therapy or who exhibit a relapse of symptoms and an increase in laboratory markers following early recovery must begin salvage therapy. It is advised that patients with non-familial diseases who have symptom remission following initial therapy cease the treatment. Only upon reactivation does treatment for these patients need to be resumed.

To prevent Pneumocystis carinii, HLH-94 advises antifungal therapy during the first round of dexamethasone therapy and ongoing cotrimoxazole treatment, which is equal to 5 mg/kg of trimethoprim three times a week.

Patients with established familial disease or persistent or relapsing nonfamilial disease should get continuation therapy and Hematopoietic cell transplantation. The regimen for continuation therapy includes daily oral Cyclosporine A (CSA) (with a target trough level of 200 µg/L), etoposide (150 mg/m2 every alternate second week), and dexamethasone pulse therapy (10 mg/m2 per day for 3 days every second week). Maintaining patients in a stable state until Hematopoietic cell transplantation is possible is the goal of continuation therapy.

Salvage Therapy
In a prospective clinical trial for adult Hemophagocytic lymphohistiocytosis, a salvage regimen consisting of liposomal doxorubicin, etoposide, and methylprednisolone (the DEP regimen) had encouraging outcomes [43].

CNS Involvement
Intrathecal (IT) methotrexate therapy is administered to patients following the HLH-94 protocol if systemic medication is not effective after two weeks or if CSF abnormalities do not improve. It is suggested to use intrathecal therapy for four doses at most (weeks three through six). <1 year: 6 mg; 1-2 years: 8 mg; 3-5 years: 10 mg; >3 years: 12 mg for each dose of methotrexate.

Conclusions
The primary challenge for individuals with Hemophagocytic lymphohistiocytosis is the significant hindrance to effective treatment and positive prognosis caused by delays in identifying the condition and initiating treatment. The delay is attributed to several reasons associated with the clinical manifestation of Hemophagocytic lymphohistiocytosis. These factors include the syndrome's infrequency, its diverse clinical presentation, and the absence of specificity in the clinical and laboratory findings. The diagnostic criteria for Hemophagocytic lymphohistiocytosis are based on the diagnostic standards of significant research.
However, these criteria may be overly strict and may not identify every patient with Hemophagocytic lymphohistiocytosis. Thus, individuals who may not meet the strict diagnostic criteria but exhibit a strong clinical suspicion for Hemophagocytic lymphohistiocytosis should receive treatment. Every patient suspected of having Hemophagocytic lymphohistiocytosis should be evaluated by a hematologist. Patients who are severely ill should be promptly transferred to an institution that offers Hemophagocytic lymphohistiocytosis therapy.

Additional Information
Disclosures

Human Subjects
Consent was obtained or waived by all participants in this study.

Conflicts of Interest
In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info
All authors have declared that no financial support was received from any organization for the submitted work.

Financial Relationships
All authors have declared that they have no financial relationships at present or within the previous three years with any or-

ganizations that might have an interest in the submitted work.

Other Relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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