International Journal of Research in Medical Sciences
Yarky A et al. Int J Res Med Sci. 2021 Dec;9(12):3705-3709
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20214724

Case Report

Hemophagocytic lymphohistiocytosis: a rare and life-threatening diagnosis

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Received: 09 October 2021
Revised: 02 November 2021
Accepted: 08 November 2021

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening syndrome of excessive activation of immune system. It frequently affects infants from birth to 18 months of age, but is also observed in children and adults of all ages. HLH can occur as a familial or sporadic disorder, and it is triggered by a variety of events, Infection being the most common trigger both in familial and in sporadic cases. Prompt treatment is very critical in cases of HLH, but the greatest barrier is often delay in diagnosis due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings. The key clinical features of HLH are high persistent fever, hepatosplenomegaly, blood cytopenia, elevated aminotransferase and ferritin levels, and coagulopathy. A diagnosis of HLH is mostly under-recognized, and is associated with high mortality, especially in adults; thus, prompt diagnosis and treatment are essential. We here present a rare case of HLH in an adult which was non-familial and infection being the trigger causing secondary hemophagocytic lymphohistiocytosis.

Keywords: HLH, Immune system, MAS

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life threatening hyperinflammatory syndrome caused by excessive activation of cytotoxic T-lymphocytes, natural killer T-cells and macrophages with subsequent cytokine storm and organ damage. It is triggered by infections and malignancies, or a combination of both in adults and leads to increased mortality.

Patients who are immunosuppressed e.g. those with autoimmune/autoinflammatory disorders are at increased risk to develop HLH which in them is also called Macrophage activation syndrome (MAS-HLH). Types of HLH are primary (familial) and secondary (acquired).

Primary HLH typically manifests in childhood, often has a family history, and is linked to mutations in genes involved in lymphocyte cytotoxicity.

Clinically, a triad of prolonged fever, hepatosplenomegaly and pancytopenia is common. HLH often is indistinguishable from sepsis or autoinflammatory diseases (e.g., adult-onset Still disease). As a result, there is high likelihood for misdiagnosing or underdiagnosing HLH.

HLH diagnosis is based on the HLH-2004 diagnostic criteria established by the Histiocyte Society. According to this criteria HLH can be diagnosed in a patient with at least 5 of 8 diagnostic criteria and/or disease-causing mutations in HLH-related genes.[1]

CASE REPORT

A 31 years old male was admitted to the medicine wards with chief complaints of loose stools and fever for 7 days. Loose stools were 3 to 4 in number daily, watery in consistency not associated with blood or mucus. There was no pain abdomen, no vomiting, no nausea, no yellowish discoloration of eyes or skin, no distension of abdomen. Fever was undocumented, low grade, not associated with chills or rigors. No past history of COVID-19, no history of vaccination against COVID-19. He had history of alcohol use disorder and consumed 60 to 80 ml of alcohol per day since last 5 years. On examination his vitals were stable and he had mild splenomegaly on per abdomen examination. Rest of the systemic examination was normal on admission.

His early baseline investigation reports were suggestive of pancytopenia, ESR=28, OT>PT=339/109, BUN=27, creatinine=2.97, sodium, potassium normal, urine proteins 3+, raised PT-INR. USG abdomen was suggestive of raised echotexture of liver and splenomegaly 12.5 cm. He was managed initially with a diagnosis of chronic liver disease; alcoholic liver disease with decompensation in the form of coagulopathy; and azotaemia (AKI vs CKD) and acute febrile illness; cause acute gastroenteritis.

Patient did not respond to the treatment and developed altered sensorium in the form of decreased responsiveness. CNS examination was normal. He developed rash over his bilateral upper and lower limbs in the form of palpable purpura and petechiae. He has an episode of Malena during his hospital stay. He tested negative for malaria, dengue, scrub typhus, leptospirosis, brucellosis, typhoid. Blood cultures and urine cultures were awaited.

In view of rash-palpable purpura, without itching, and was sent in view of connective tissue disorder. He was managed with injection doxycycline, injection cefepime and injection azithromycin. His platelet count decreased to 3000, serum ferritin was >2000, TG was 189 and upper GI endoscopy revealed few antral erosions and no varices. He was transfused with platelets, whole blood and fresh frozen plasma. Meanwhile, pyrexia persisted, cytopenia persisted, patient developed tachypnoea and unilateral crepitations in his chest.

Fibrinogen and FDPs were sent in view of DIC picture and Soluble CD25 and NK cell activity was sent in view of HLH. Soon the patient started feeling better symptomatically. Fever subsided, rash also subsided, blood and urine cultures came back sterile. Sputum cultures had growth of Acinetobacter baumanii.

Procalcitonin was 17.6, FDP and fibrinogen reports were normal. NK activity was negative and Soluble CD25>2400 U/ml. Bone marrow aspiration and biopsy revealed infiltration of bone marrow by activated macrophages consistent with hemophagocytosis. patient responded to the antibiotics considering the cause of secondary HLH was infection-pneumonia and was discharged in stable condition.

DISCUSSION

HLH is a severe hyperinflammatory syndrome characterised by a dysregulated immune response due to various triggers. As there is no systematic data for adult recommendations of HLH's diagnosis and management, recommendations have been adopted from paediatric guidelines (Table 1). These guidelines are helpful in some cases but still raise many challenges. One such challenge is that patients may present with sepsis and may undergo overtreatment and unnecessary toxicity as the treatment algorithms are frequently based on paediatric protocols, such as HLH-94 and HLH-2004.Therefore, dose reductions, individualized treatment, duration, and an age-dependent modified diagnostic approach are needed.[2]

Overview and indications of treatment

HLH is an aggressive syndrome and if left untreated, patients with HLH survive for only a few months, due to MODS. In 1994, the Histiocyte Society organized the first treatment protocol for HLH (HLH-94).[3,4] There are many barriers in the early diagnosis and treatment of HLH such as varied clinical presentation of HLH, rarity of the syndrome and the lack of specificity of the clinical and laboratory findings.

The goal of therapy is to suppress life-threatening inflammation. Induction therapy based on the HLH-94 protocol consists of a series of weekly treatments with dexamethasone and etoposide .
Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease. After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic Hematopoietic cell transplantation (HCT). HCT is needed in those with an HLH gene mutation, CNS disease or relapse. In 2004, a new HLH protocol was initiated (HLH-2004) with major modifications to use cyclosporine early and to add hydrocortisone to the intrathecal methotrexate.

If a patient is clinically stable and the ferritin is consistently below 10,000 ng/ml or rises from 1000 to 3000 ng/ml with only slightly elevated D-dimer and liver enzymes, treatment need not be started. However, if those two parameters become progressively more abnormal, early initiation of at least dexamethasone is required. For patients who have a triggering infection, like in our patient or rheumatologic condition, treatment of the triggering condition should be initiated simultaneously with HLH-specific chemotherapy. When HLH is triggered by an acute infection or other condition (e.g. rheumatologic condition), appropriate treatment of the trigger may remove the stimulus for immune activation. Patients who are less acutely ill like in this case our patient whose ferritin levels were well below 10,000 and d dimer and

liver enzymes were only slightly elevated and he was clinically stable, such patients tolerate treatment of the infection/sepsis alone without HLH-specific therapy; thus, avoiding the potentially toxic therapy.

Pre-therapy testing which is performed in all patients includes

HLA typing and search for an HCT donor- patients with HLH gene mutations, hematologic malignancy, relapsing symptoms on or off therapy, and/or central nervous system disease will require HCT. Because the response to therapy is not known at the time therapy is started, all patients and appropriate family members should undergo HLA typing to facilitate identification of an HCT donor.

Cardiac function

A baseline evaluation of cardiac function) prior to starting chemotherapy is performed.

Disease markers

Baseline immunologic studies [e.g. soluble IL-2 receptor alpha (sCD25), soluble haemoglobin-haptoglobin scavenger receptor (sCD163)] as well as other markers of disease activity (e.g. complete blood count, ferritin, fibrinogen, D-dimer, liver function tests) are done.

Clinically stable patients

Overview (clinically stable)

Patients who are clinically stable and have a triggering condition responsible for HLH (e.g. infection, rheumatologic condition) may respond to treatment of the condition alone. If there is any deterioration during the investigation for cause of HLH, it is an indication to start HLH-specific therapy immediately.

Empiric antibiotic, antifungal, antiviral, or antiparasitic therapy should be initiated depending on the suspected organism(s). Patients who are clinically stable and respond rapidly to treatment of the infection may be able to avoid HLH-specific chemotherapy.

Some patients with an underlying immunosuppressive condition respond to disease-specific therapy. Example if a patient of rheumatoid arthritis is stable enough to delay HLH-specific therapy, he should be treated with a course of corticosteroids and/or other therapy for the underlying condition.

Acutely ill or deteriorating patients

Patients with HLH who have multi organ dysfunction (e.g. cardiovascular, pulmonary, renal, hepatic, or neurologic) should be treated immediately with HLH-specific treatment based on the HLH-94 protocol. More than half of patients treated with the HLH-94 regimen achieve five-year survival.

With such patients, there is typically concordance between clinical findings and laboratory abnormalities (e.g. rising serum ferritin, D-dimer, liver enzyme, sCD25, or sCD163 levels).

Therapy based on the HLH-94 protocol consists of eight weeks of induction therapy with etoposide (VP-16) and dexamethasone, with intrathecal therapy for those with CNS involvement.

VP-16 is given at a dose of 150 mg/m^2 for adults. The dose is given twice weekly for the first two weeks, and once weekly for weeks three through eight. Dexamethasone is the preferred corticosteroid because it can cross the blood-brain barrier. Dexamethasone is given intravenously or orally and tapered over the eight-week induction. When patients do not show a response to this therapy within two to three weeks; salvage therapy should be considered.

The response to initial therapy is a major factor in determining the need for additional therapy including HCT. Response to induction therapy is monitored by assessing the patient clinically and using HLH disease-specific markers, which are: (a) physical examination focused on temperature, rashes, lymphadenopathy, hepatosplenomegaly, neurologic findings, and organ-specific findings noted on presentation; (b) complete blood count with differential; (c) coagulation studies including PT, aPTT, fibrinogen, and D-dimer; (d) ferritin, renal function, and electrolytes if previously abnormal; (e) liver function tests including ALT, AST, total bilirubin, GGT, and LDH; and (f) CSF analysis for those with neurologic or CSF abnormalities.

For the most of the patients, these parameters will identify organ involvement and tell us about the response to therapy. We also monitor disease-specific markers like Lymphocyte and cytokine markers [e.g. soluble IL-2 receptor alpha (sCD25), soluble haemoglobin-haptoglobin scavenger receptor (sCD163)], serum ferritin, NK cell function and viral titres.

Prognosis

Despite the significant improvement in survival with the HLH-94 protocol, mortality with HLH remains high. The ideal form of immune suppression/anti-inflammatory therapy is still unknown. Although somewhat responsive to corticosteroids and clearly responsive to etoposide or anti-T-cell serotherapy (ATG or alemtuzumab), HLH is difficult to treat. Future studies will focus on defining which immune-modulating strategies offer the best balance of safety and efficacy.[5] Hemophagocytic lymphohistiocytosis is treated with immune suppressants, etoposide, and allogeneic hematopoietic stem cell transplantation; more than 50% of children who undergo transplant survive, but adults have quite poor prognosis

even with aggressive management. Newer agents directed at overcoming the uncontrolled immune response in a targeted fashion offer promise in this highly morbid disease.[6] In COVID-19 patients, secondary HLH and cytokine storm are responsible for unexplained progressive fever, cytopenia, ARDS, neurological and renal impairment. Differentiation between the primary and secondary forms of HLH is very important, since primary form of HLH requires complicated treatments such as hematopoietic stem cell transplantation. Further studies addressing the performance of HS score and other recommendations in the classification of these patients is necessary.[7]

Table 1: HLH 2004 diagnostic criteria according to Henter et al (2007).

At least one of either (1) or (2) must be fulfilled:	
Molecular diagnosis consistent with HLH	
At least 5 out of the 8 of the following criteria:	
Fever	
Cytopenia of two or more lineages	Hb<90 g/l
	ANC<1×10^9/l
	Platelets<100×10^9/l
Splenomegaly	
Hypertriglyceridemia and/or hypofibrinogenemia	Fasting triglyceride≥3 mmol/l
	Fibrinogen<1.5 g/l
Hyperferritinemia	Ferritin≥500 ug/l
Elevated Sil-2R(sCD25)	sIL-2R≥2400 U/ml
Low or absent NK-cell activity	
Hemophagocytosis in bone marrow, spleen or lymph node	

Note: ANC- Absolute neutrophil count, sIL-2R- Soluble interleukin-2 receptor, NK-cell- Natural killer cell.

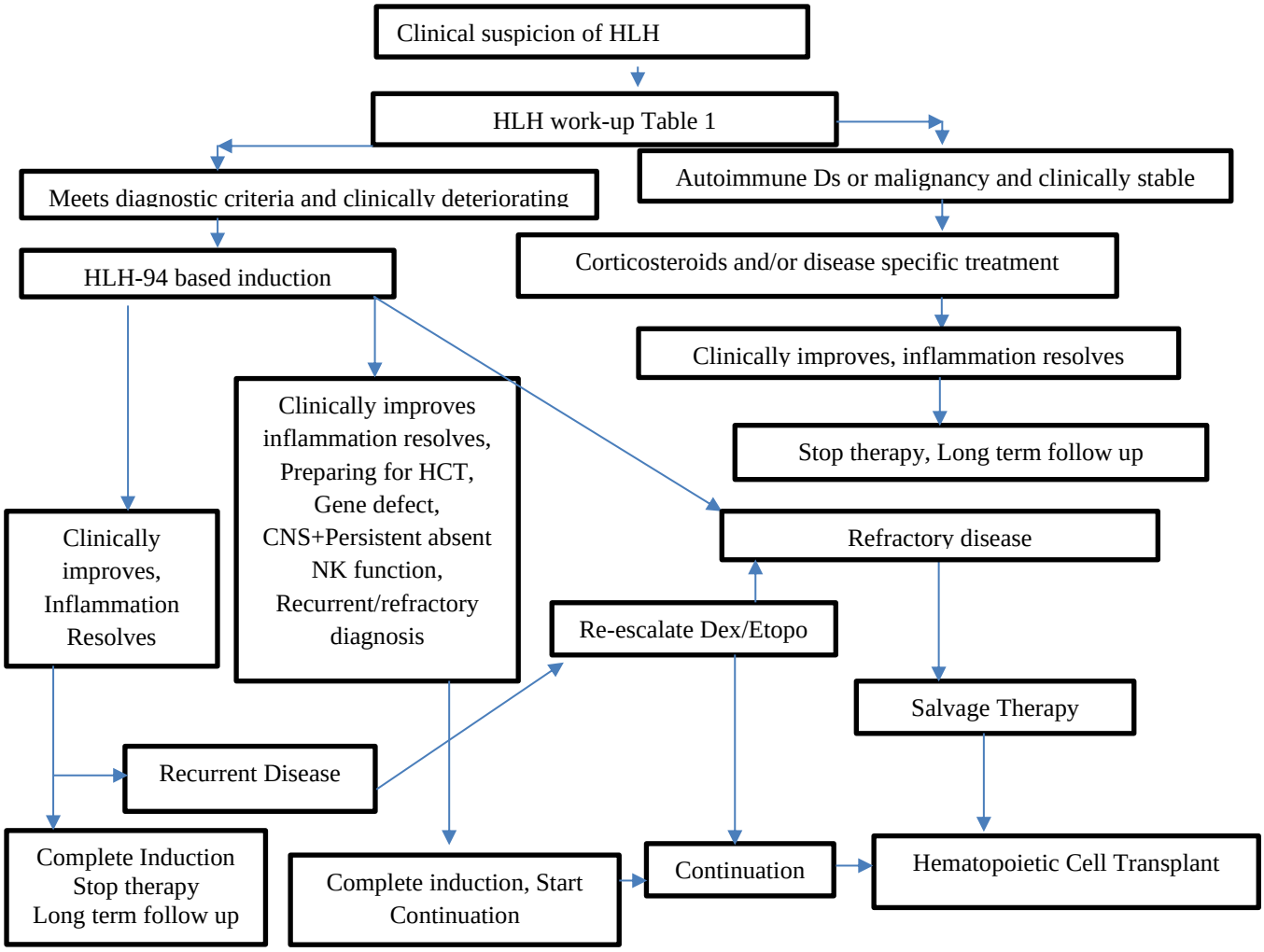

Figure 1: Flowchart of management of HLH.

CONCLUSION

HLH is a varied condition with many causes and is mostly under-recognized, which contributes to its high morbidity and mortality. Early recognition is crucial for a timely curative therapy. HLH-94, HLH-2004 treatment regimens followed by HSCT have greatly increased survival in this aggressive disease. A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment options; however, much work remains to raise awareness and improve the effectiveness of treatment regimens.

ACKNOWLEDGEMENTS

We would like to thank the patient for cooperating with us and giving us consent for publishing his data and we would like to thank the department of Medicine for its support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Yarky A, Kumar V, Chauhan N, Verma N. Hemophagocytic lymphohistiocytosis: a rare and life-threatening diagnosis Int J Res Med Sci 2021;9:3705-9.