Ref: Ro J Rheumatol. 2024;33(2)
DOI: 10.37897/RJR.2024.2.4

An uncommon diagnosis of a young female with fever of unknown origin (FUO): Idiopathic Hemophagocytic Lymphohistiocytosis (HLH)

Amukthamalyada Koduri[1], Anuhya Adusumilli[2], Ramkumar Murali[3], Magesh Kumar S.[3]

[1]Saveetha Medical College, Chennai, Tamilnadu, India
[2]Sree Balaji Medical College and Hospital, Chennai, Tamilnadu, India
[3]Department of General Medicine, Saveetha Medical College, Chennai, Tamilnadu, India

ABSTRACT

Background. Hemophagocytic Lymphohistiocytosis (HLH), characterized by uncontrolled activation of immune cells leading to a hyperinflammatory state, is seldom considered in the initial differential diagnosis of FUO. The rarity of idiopathic HLH, especially in young individuals without an identifiable trigger, emerges as an uncommon and particularly challenging diagnosis. This case report presents a compelling narrative of a young female grappling with the complexities of FUO, ultimately revealing the rare and life-threatening entity of idiopathic HLH.

Case report. A 25 year old female was referred to our hospital in view of persistent high grade fever since 3 months. Patient has no other complaints. Vitals stable. General and systemic examination normal. Lab investigations showed a total leukocyte count 18000 cell/µL, hemoglobin 9.2 g/dL, and platelets 68000 cells/µL. Other blood investigations showed erythrocyte sedimentation rate (ESR) 88 mm/h, C-reactive protein 21 mg/L, ferritin 670 ng/mL, triglyceride 281 mg/dL, and fibrinogen 1.2g/L. She also had transaminitis with AST 80, ALT 92 and ALP 1442. The entire infectious diseases panel was done which came negative for all, including viral serologies and hepatitis markers. Procalcotonin level was normal and no other relevant investigations came positive. Autoimmune panel analysis also came negative. Blood cultures came negative in two different samples. Also, there is no evidence of vegetation in echocardiography. Coming to the invasive investigations, bone marrow biopsy and aspiration were done to arrive at a diagnosis and it showed Hemophagocytosis. Endoscopy and colonoscopy were done, which came normal. CT thorax and abdomen also showed no significant abnormality, ruling out the probability of missing any gross malignancies. After all this extensive work up and according to Hscore, which is used to estimate an individual's risk of having reactive hemophagocytic syndrome, this patient was diagnosed with HLH. According to the current HLH guidelines, initial treatment for the disease consists of etoposide, corticosteroids (dexamethasone), or cyclosporine is given for 8 weeks. The patient was started on the same above treatment regimen, but only with corticosteroids for a period of 8weeks, after consultation with Hematologist. No recurrence is seen in her 6-months of follow-up. The regimen was well tolerated by the patient. Studies also have shown that therapeutic plasma exchange also has a role in HLH treatment, which can be tried in familial and relapsing cases.

Conclusion. In our case, this young female was diagnosed to have Idiopathic HLH, after ruling out all the familial and secondary causes of HLH including Infections, Malignancy and Autoimmune diseases. The patient was also started on treatment early after the bone marrow and other relevant investigations according to HScore suggested the diagnosis of HLH and the patient improved accordingly. Hence, apart from clearly knowing the etiology or clinical manifestations, HLH is associated with a high mortality rate if appropriate treatment not given. Generally, the underlying etiology determines the prognosis of the disease. But, it is not a good idea to delay the treatment in order to find the cause and type of HLH, because the exhaustive work up might lead to unacceptable delays in improvement and prognosis of the patient. The diagnostic work up and treatment should be done simultaneously in the patient, which has been done in our case and it lead to a good outcome. Though HLH is a fatal and dangerous disease and also highly challenging to make a diagnosis due its uncommon and largely variable clinical presentation, smart work up and early initiation of treatment will lead to better prognostic outcome.

Keywords: HLH, fever of unknown origin, young female, idiopathic

Corresponding author:
Amukthamalyada Koduri
E-mail: aamuktak96@gmail.com

Article History:
Received: 19 May 2024
Accepted: 28 June 2024

Abbreviations (in alphabetical order):

ALP – Alkaline phosphatase
ALT – Alanine transaminase
AST – Aspartate transaminase
ESR – Erythrocyte sedimentation rate
FUO – Fever of unknown origin
HLH – Hemophagocytic lymphangiocytosis

INTRODUCTION

The diagnostic challenge posed by Fever of Unknown Origin (FUO) is an intricate puzzle that necessitates a thorough investigation to unveil the underlying etiology, as the spectrum of causative factors widens to include infectious, inflammatory, neoplastic, and hematologic etiologies.

Hemophagocytic Lymphohistiocytosis (HLH) [1,2], characterized by uncontrolled activation of immune cells leading to a hyperinflammatory state, is seldom considered in the initial differential diagnosis of FUO. The rarity of idiopathic HLH, especially in young individuals without an identifiable trigger, emerges as an uncommon and particularly challenging diagnosis, especially when encountered in young individuals.

There are inherited and non-inherited (acquired) causes of hemophagocytic lymphohistiocytosis (HLH). There are 2 types of HLH: familial and acquired. Familial HLH accounts for about 25% of cases and passes down the generations. If both parents are HLH genetic carriers, a child has a 25% chance of getting the disease, a 25% chance of not getting the disease, and a 50% chance of being a carrier [3]. A number of secondary conditions cause acquired HLH. These include:

- Viral infections, mainly Epstein-Barr virus
- Other systemic infections
- Immunocompromised states
- Malignancy

This case report presents a compelling narrative of a young female grappling with the complexities of FUO, ultimately revealing the rare and life-threatening entity of idiopathic HLH.

CASE PRESENTATION

A 25 year old female was referred to our hospital in view of persistent fever of high grade since 3 months. On admission, she was febrile with body temperature of 102F. Other vitals were normal. The patient had no symptoms of respiratory or urinary etiology. Other physical examination was normal.

Lab investigations showed a total leukocyte count 18000 cell/µL, hemoglobin 9.2 g/dL, and platelets 68000 cells/µL. Other blood investigations showed erythrocyte sedimentation rate (ESR) 88 mm/h, C-reactive protein 21 mg/L, ferritin 670 ng/mL, triglyceride 281 mg/dL, and fibrinogen 1.2g/L. She also had transaminitis with AST 80, ALT 92 and ALP 1442.

The entire infectious diseases panel was done which came negative for all, including viral serologies and hepatitis markers. Procalcotonin level was normal and no other relevant investigations came positive. Autoimmune panel analysis came all negative. Blood cultures came negative in two different samples. Also, there is no evidence of vegetation in echocardiography.

Coming to the invasive investigations, bone marrow biopsy and aspiration were done to arrive at a diagnosis and it showed hemophagocytosis. Endoscopy and colonoscopy were done, which came normal. CT thorax and abdomen also showed no significant abnormality, ruling out the probability of missing any gross malignancies.

After all this extensive work up and according to HScore, which is used to estimate an individual's risk of having reactive hemophagocytic syndrome, this patient was diagnosed with HLH (Tables 1, 2).

According to the current HLH guidelines, initial treatment for the disease consists of etoposide, corticosteroids (dexamethasone) or cyclosporine is given for 8 weeks. Hence, after consultation with hematologist, our patient was also started on the same treatment regimen, but only with corticosteroids i.e, PULSE therapy was given for 3 days with Inj Dexamethasone 10 mg/kg for 5 days followed by Tab Dexamethasone 5 mg/kg for 2 weeks, then tapered to 2.5 mg/kg for 2 weeks, then 1.25 mg/kg for 1 week and one week OD tapering done, accounting totally for a period of 8 weeks.

The patient started improving in 3 days, i.e, number of fever spikes and grade of fever reduced. The patient became completely afebrile. No recurrence was seen in her 6-months of follow-up. The regimen was well tolerated by the patient.

DISCUSSION

In most of the cases, the actual etiology of HLH is not clear, hence making it pretty difficult for diagnosis. Because it has no unique clinical, biologic, or histologic features, reactive hemophagocytic syndrome may be difficult to distinguish from other diseases such as severe sepsis or hematologic malignancies.

But, according to the HS score [4] which is developed recently in 2014 for knowing the probability of developing HLH in adults, it has become a lesser hassle in arriving at the diagnosis of HLH. A score of around more than 200 obtained by calculating the

TABLE 1. HScore for reactive Hemophagocytic syndrome

Criteria			
1. Known underlying immunosuppression HIV positive or receiving long-term immunosuppressive therapy (i.e.,Glucocorticoids, Cyclosporine, Azathioprine)	NO (0)	YES(+18)	
2. Temperature, °F	<101.1(0)	101.1-102.9 (+33)	>102.9(+49)
3. Organomegaly (hepatomegaly or splenomegaly)	NO (0)	Any 1(+23)	Both(+38)
4. Number of cytopenias (Defined as hemoglobin ≤9.2 g/dL (≤5.71 mmol/L) and/or WBC ≤5,000/mm³ and/or platelets ≤110,000/mm³)	1 lineage (0)	2 lineages (+24)	3 lineages (+34)
5. Ferritin, ng/mL (or µg/L)	<2000(0)	2000-6000 (+35)	>6000(+50)
6. Triglyceride, mg/dL	<132.7(0)	132.7-354 (+44)	>354(+64)
7. Fibrinogen, mg/dL(g/L)	>250/>2.5(0)	</=250/2.5 (+30)	
8. AST (U/L)	<30(0)	>/=30(+19)	
9. Hemophagocytosis features on bone marrow aspirate	NO (0)	YES (+35)	

Interpretation:

HScore	**Probability of Hemophagocytic Syndrome**
≤90	<1%
91-100	~1%
101-110	1-3%
111-120	3-5%
121-130	5-9%
131-140	9-16%
141-150	16-25%
151-160	25-40%
161-170	40-54%
171-180	54-70%
181-190	70-80%
191-200	80-88%
201-210	88-93%
211-220	93-96%
221-230	96-98%
231-240	98-99%
≥241	>99%

Note: the best cutoff value for HScore was 169, corresponding to a sensitivity of 93%, specificity of 86%, and accurate classification of 90% of the patients.

criteria in this score, would account to around 80% probability of developing HLH. Accordingly, the patient in our case obtained a score of 208, which indicates 88-93% probability of having HLH.

Prolonged fever with an unknown origin can be the initial or the only manifestation in HLH patients. Assessment of a patient presenting with FUO is usually very challenging. Whereas, causes of FUO, like the HLH etiology, are very similar; this makes it very difficult in deriving the underlying diagnosis, thus resulting in rapid diagnosis and treatment to prevent bad consequences.

In our case, treatment was started early and simultaneously extensive work up was continued. Genetic testing couldn't be done in our patient due to financial constraints of the patient. But, since all the other autoimmune, malignant, panel for infections, invasive studies like endoscopy and colonoscopy, echocardiogram, imaging like CT thorax and abdomen turned out to be normal, we arrived at the diagnosis of Idiopathic HLH for our patient [5].

TABLE 2. HScore diagnostic criteria and clinical findings of the patient

2014 HScore diagnostic criteria	**Clinical findings of the patient**	
1. Known underlying immunosuppression HIV positive or receiving long-term immunosuppressive therapy (i.e.,Glucocorticoids, Cyclosporine, Azathioprine)	No	**(0)**
2. Temperature, °F	102°F	**(+33)**
3. Organomegaly (hepatomegaly or splenomegaly)	Splenomegaly present	**(+23)**
4. Number of cytopenias (Defined as hemoglobin ≤9.2 g/dL (≤5.71 mmol/L) and/or WBC ≤5,000/mm³ and/or platelets ≤110,000/mm³)	Hb-8.2, WBC-10800, Platelets- 73000 2 lineages present	**(+24)**
5. Ferritin, ng/mL (or µg/L)	670 ng/mL	**(0)**
6. Triglyceride, mg/dL	281mg/dL	**(+44)**
7. Fibrinogen, mg/dL(g/L)	1.2 g/L	**(+30)**
8. AST (U/L)	80 U/L	**(+19)**
9. Hemophagocytosis features on bone marrow aspirate	Yes	**(+35)**

The total score amounts to 208 points, hence the probability of Hemophagocytic syndrome in this patient is 88-93%

According to the recent HLH treatment guidelines, initial treatment for the disease consists of etoposide, corticosteroids (dexamethasone), or cyclosporine, given for 8 weeks [6]. In previously reported cases, corticosteroids are used as the first line of treatment. So, in this case also after consulting hematologist, patient was treated with dexamethasone and the patient showed response.

Normally the above initiation therapy treatment is sufficient. But, continuation therapy should be given in patients with proven familial disease or persistent or relapsing non-familial disease [7]. Since our patient recovered well and showed no relapses, no further treatment was done.

Some studies also show that Therapeutic plasma exchange [8] has a role in treatment of HLH. It has been shown to improve the clinical and laboratory findings of HLH by reducing the circulating inflammatory mediators. It also has been shown to increase the response to steroids by reducing IL-6 and TNF-alpha levels. So, it can be tried in patients who don't show adequate response to medications.

CONCLUSION

In our case, this young female was diagnosed to have idiopathic HLH, after ruling out all the familial and secondary causes of HLH including infections, malignancy and autoimmune diseases. The patient was also started on treatment early after the bone marrow and other relevant investigations according to HScore suggested the diagnosis of HLH and the patient improved accordingly.

Hence, apart from clearly knowing the etiology or clinical manifestations, HLH is associated with a high mortality rate if appropriate treatment not given. Generally, the underlying etiology determines the prognosis of the disease. But, it is not a good idea to delay the treatment in order to find the cause and type of HLH, because the exhaustive work up might lead to unacceptable delays in improvement and prognosis of the patient.

The diagnostic work up and treatment should be done simultaneously in the patient, which has been done in our case and it lead to a good outcome. Though HLH is a fatal and dangerous disease and also highly challenging to make a diagnosis due its uncommon and largely variable clinical presentation, smart work up and early initiation of treatment will lead to better prognostic outcome.

Patient consent:
A clear informed consent obtained from patient and patient attenders

Conflicts of interest: none declared

Financial support: none declared

Author's contributions:
Amukthamalyada Koduri and Anuhya Adusumilli have contributed to the data collection, initiation of treatment, follow-up and preparation of manuscript (writing and draft)
Ramkumar Murali and Magesh Kumar S. contributed to review and finalisation of manuscript.
All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. *Annu Rev Pathol.* 2018 Jan 24;13:27-49. doi: 10.1146/annurev-pathol-020117-043625. Epub 2017 Sep 13. PMID: 28934563.
2. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol.* 2013 Jun;139(6):713-27. doi: 10.1309/AJCP4ZDKJ4ICOUAT.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014 Apr 26;383(9927):1503-1516. doi: 10.1016/S0140-6736(13)61048-X. Epub 2013 Nov 27. Erratum in: *Lancet*. 2014 Apr 26;383(9927):1464. PMID: 24290661.
4. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol.* 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690. PMID: 24782338.
5. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007 Feb;48(2):124-31. doi: 10.1002/pbc.21039. PMID: 16937360.
6. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019 Jun 6;133(23):2465-2477. doi: 10.1182/blood.2018894618. Epub 2019 Apr 16. PMID: 30992265.
7. Wang Y, Huang W, Hu L, Cen X, Li L, Wang J, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. *Blood*. 2015 Nov 5;126(19):2186-92. doi: 10.1182/blood-2015-05-644914. Epub 2015 Aug 19. PMID: 26289641; PMCID: PMC4635114.
8. Bosnak M, Erdogan S, Aktekin EH, Bay A. Therapeutic plasma exchange in primary hemophagocytic lymphohistiocytosis: Reports of two cases and a review of the literature. *Transfus Apher Sci.* 2016 Dec;55(3):353-356. doi: 10.1016/j.transci.2016.09.015. Epub 2016 Sep 28. PMID: 27743708.