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

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WORD COUNT 1223 TIME SUBMITTED 21-MAY-2024 03:38PM

PAPER ID 109115233

Word Count – Words: 1,223

TYPE OF ARTICLE: Case Report

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

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ABSTRACT

Background. 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.
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.
Blood cultures came negative in two different samples. The bone marrow examination showed Hemophagocytosis. Autoimmune panel analysis came negative. Finally, on excluding all other differentials, and according to the clinical features and laboratory results that met the HLH-diagnostic criteria 2004, the diagnosis of idiopathic HLH was done [3-5].
According to the 2004-HLH guidelines, initial treatment for the disease consists of etoposide, corticosteroids (dexamethasone), or cyclosporine, given for 8weeks.

Conclusion. 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. It is a fatal and dangerous disease and also highly challenging to make a diagnosis due its uncommon and largely variable clinical presentation.

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

Abbreviations:

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

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 hyper inflammatory 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.
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 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 680** ng/mL, triglyceride 282 mg/dL, and fibrinogen 123 mg/dL. She also had transaminitis with AST 80, ALT 92 and ALP 1442.
Blood cultures came negative in two different samples. Also, there is no evidence of vegetation in echocardiography. So, to arrive at a diagnosis, bone marrow biopsy and aspiration were done and they showed **Hemophagocytosis**. Endoscopy and colonoscopy were done, which came normal.
Autoimmune panel analysis came all negative. Finally, on excluding all other differentials, and according to the clinical features and laboratory results that met the HLH-diagnostic criteria 2004, the diagnosis of idiopathic HLH was done [3]. The patient was started on treatment with steroids (dexamethasone). No recurrence 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. According to the 2004-HLH guidelines, either molecular detection of MLH-compliant factor or at least 5 out of 8 criteria should exist for making the HLH diagnosis [4,5]. Accordingly, the patient in our case fulfilled 5 criteria, hence diagnosed as idiopathic HLH.
Hemophagocytosis outcome in bone marrow biopsy is not necessary for the diagnosis. 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.
According to the given guidelines, initial treatment for the disease consists of etoposide, corticosteroids (dexamethasone), or cyclosporine, given for 8weeks. In previously reported cases, corticosteroids are used as the first line of treatment. So, in this case after consulting hematologist, patient was treated with dexamethasone and the patient showed response.

CONCLUSION

Apart from clearly knowing the etiology or clinical manifestations, HLH is associated with a high mortality rate if appropriate treatment not given. In general, the underlying etiology determines the prognosis of the disease. It is a fatal and dangerous disease and also highly challenging to make a diagnosis due its uncommon and largely variable clinical presentation.
And the important problem in initiation of treatment is the delayed diagnosis. Treatment should be given based on the clinical condition of the patient and underlying suspected causes.

Patient consent:

Word Count – Words: 1,223

A clear informed consent obtained from patient and patient attenders

Conflicts of interest: Nil

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

Acknowledgements: Nil

TABLES

Table 1: 2004-HLH Diagnostic Criteria and Clinical Findings of the Patient:

2004-HLH diagnostic criteria	clinical findings of the patient
Fever	Present
Splenomegaly	Present
Cytopenia(>2 of 3 lineages)	Not done
Hemoglobin <9g/dL	8.2g/dL
Neutrophil < 1x109cells/L	10800/mm3
Platelet < 100x10 power 3 cells/L	73000/mm3
Hypertriglyceridemia or hypofibrinogenemia	Both present
Fasting triglyceride ≥ 265 mg/dL	281ng/mL
Fibrinogen < 1.5g/L	1.2g/L
Low NK cell activity	Not done
Ferritin > 500ng/mL	670ng/mL
Soluble IL-2 > 2400U/mL	Not done

Hemophagocytosis in bone marrow, spleen or lymph nodes	No hemophagocytosis

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