(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 6 , Page No: 94-99
November-December 2023

IJMSCR

Secondary Hemophophagocytic Lymphohistiocytosis - A Diagnostic Dilemma (Rare Case Report)

[1]Dr. Sangeeta Hudda , [2]Dr. Jyoti Pandey, [3]Dr. Pankaj Kaler, [4]Dr. Manju Raghava
[1,2,4]MD (Pathology), [1]Assistant Professor , [2]Senior Resident,
[3]MD (Radiodiagnosis), Consultant, [4]Professor and Head
[2]MDBASMC, Deoria, Uttar Pradesh
[1,4]Department of Pathology, MGUMST, Jaipur

***Corresponding Author:**
Dr. Sangeeta Hudda
204C, Balaji Majestic Society (Tower 9), Jagatpura, Jaipur, 302017

Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a serious disease caused due to over-activation immune system. HLH is tough to diagnose and is usually diagnosed at late stage which leads to high mortality. Preceding factors may be viral infections, comorbidities, or malignancies. It has very poor prognosis if left untreated, with survival of only a few months and is mostly refractory to treatment.

Our case report presents a 56-year-old male who presented three weeks after COVID-19 infection with extreme fatigue, fever, lab work concerning for HLH, and biopsy indicating a high probability of HLH. Early diagnosis of HLH can be made possible by including ferritin, triglyceride and fibrinogen level to routine investigation in febrile patient of no clear etiology.

Keywords: Immune activation, Multisystem involvement, Pyrexia of unknown origin, Post covid-19 manifestations, Secondary Hemophagocytic lymphohistiocytosis (HLH).

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a serious, hyper-inflammatory disorder affecting both neonate and adults .The disorder is characterized by dysregulated immune system resulting in hyper inflammation and multi-organ failure.The inflammatory process is associated with uncontrolled macrophage activation and the release of a large number of cytokines, which is responsible for heterogeneous syndrome's clinical presentation. The main features of includes fever, hepato-splenomegaly, pancytopenia, and coagulopathy.[1] HLH could be secondary to infections: viral, fungal, and bacterial; malignancies and autoimmune diseases. The diagnosis of HLH is usually missed due to the presence of vague symptomatic presentation. This contributes to higher chances mortality.[2] In COVID-19 patients, secondary HLH and cytokine storm may be responsible for unexplained progressive fever, cytopenia, multi organ involvement like ARDS, neurological and renal impairment.

AIM OF STUDY: Our report is based on a patient who was diagnosed with secondary HLH after being recovered from COVID-19 infection. The study aims to increase the awareness about the underdiagnosed complications of COVID-19 i.e. secondary HLH, cytokine release syndrome.

Table 1 .Diagnostic criteria for HLH (five out of the eight criteria below should be present to diagnose HLH)

1. Splenomegaly
2. Fever

3. Cytopenias affecting two or three lineages
    1. Platelets <100 x 10^9/L
    2. Hemoglobin <9.0 g/dL (<10.0 g/dL in infants younger than four weeks)
    3. Neutrophils <1.0 x 10^9/L
4. Hypertriglyceridemia

    Fasting triglycerides ≥3.0 mmol/L (≥265 mg/dL)
5. Hypofibrinogenemia

    Fibrinogen ≤1.5 g/L
6. Hemophagocytosis in bone marrow, spleen, or lymph nodes
7. Ferritin ≥500 µg/L Soluble CD25 (soluble IL-2 receptor) ≥2,400 U/ml

Case Report

A 56-year-old male weighing 79 kg presented with a history of diarrhea and weight loss since 16 days. Vitals were stable. All the viral markers which includes Mycobacterium TB PCR(Genexpert), HbsAg, Anti HCV antibody, Anti HIV I and II antibody, Anti-HEV IgM, Anti-HAV IgM were Non-reactive , stool and urine culture were negative. On Colonoscopic biopsy, he was diagnosed with acute infective colitis. After 1 month (April,2023) he developed cough , on and off diarrhea , mild fever and severe weakness with significant weight loss of 11 kgs. On HRCT and RT PCR, patient was found to be Covid positive with CORADS Score 11/25 (moderate).Patient was managed & treated with remdesivir and molnupiravir. 3 weeks after COVID-19 infection ,the patient presented to the emergency department with a four day history of fever up , dry cough and further weight loss of 5kg (63kg) . Laboratory studies on admission were significant with high Aspartate Aminotransferase (AST) ,Alanine Aminotransferase (ALT) and C-reactive protein (CRP).Respiratory viral panel testing for respiratory syncytial virus, influenza, and COVID-19 was negative. CT Chest and abdomen revealed flare up of the ground glass opacities, consolidation, enlarged axillary, mediastinal and mesenteric lymph nodes. Mesenteric lymph nodes Biopsy - Necrotising histiocytic lymphadenitis suggestive of viral lymphadenitis. Ki67 index was 85%, CD3 Positive and other markers were negative.

These findings were inconclusive to give lymphoma or viral lymphadenitis and was suggested to shift patient to higher Centre for further work up. There,the condition of patient started deteriorating so a differential of hemophagocytic lymphohistiocytosis was suspected based on lab tests. Repeat mesenteric lymph node biopsy, PET- CT and bone marrow biopsy was done at higher center ,on the diagnosis of HLH, all antibiotics were replaced by antiviral gancyclovir, and the patient was treated with guideline-based immuno-chemotherapy with dexamethasone and etoposide for HLH. As the patient was refractory to treatment and was in metabolic acidosis, deranged LFT so he was kept on Continuous renal replacement therapy (CRRT) and passed away due to deteriorating condition.

Table 2 Patient blood investigation on higher center

	During hospitalization				
Laboratory test	Day 5 (10/5/2023)	Day 6 (11/5/2023)	Day 7 (12/5/2023)	Day 8 (13/5/2023)	Day 9 (14/05/2023)
Hemoglobin, g/dL	10.9	10.5	8.6	7.6	7.7
White blood cell count, $10^{3/}$uL	5.95	4.52	2.32	3.40	0.98
Platelet count,10^3/ul	120	90	50	39	31
Alanine aminotransferase, U/L	281	313	288	331	354

Volume 6, Issue 6; November-December 2023; Page No 94-99

Aspartate aminotransferase, U/L	756	976	1063	1361	1472
Bilirubin Total,mg/dl	6.15	7.81	8.70	9.98	6.19
C-reactive protein, mg/L	111.6				
Gamma GT , U/L	905	853	634	650	415
Alkaline phosphatase ,U/L	613	693	576	711	484
Blood urea, mg/dl	130	68	128	69	75
Serum Creatinine,mg/dl	2.30	1.40	2.50	1.50	1.60
Uric acid(serum),mg/dl	6.9	3.3	5.8	3.8	4.8
FERRITIN ,ng/ml	46300 (H)	49500	60500	80300	84100
TRIGLYCERIDES ,mg/dl	374 (H)				
LDH , U/L	3516 (H)	3889	4197	7381	5202
FIBRINOGEN ,mg/dl	93.7 (L)		51.9	41	
IL-6 cytokine assay, pg/ml	59.98			422.4	2015

PET - CT Revealed intense FDG uptake in spleen, mucosal thickening at posterior pharyngeal wall and multiple enlarged cervical, mediastinal, axillary ,mesenteric(largest) lymph nodes seen.

Mesentric lymph node core biopsy

1. Predominantly interfollicular T lymphoid cells with histiocytes , plasmacytoid dendritic cells and plasma cells -.On IHC -
2. CD20: Positive in few B lymphoid cells
3. CD3:Positive in interfollicular T cells
4. CD21, S100 ; Negative
5. CD68 :Positive
6. CD8>CD4
7. CD7,CD2,CD5 ,bcl2- Positive in interfollicular T cells
8. MUM 1 and CD30: Positive in immunoblasts
9. Impression- Necrotising histiocytic lymphadenitis suggestive of viral lymphadenitis

Bone Marrow Biopsy-

1. CD 3 and 20: Few individually scattered T and B lymphocytes in marrow interstitium (T>B)
2. CD68: Prominence of histiocytes
3. CD 34: No evidence of blast
4. PAS & GMS- No fungal elements seen
5. AFB: Negative
6. Impression-Prominence of histiocytes, several showing features of hemophagocytosis of RBCs, WBCs and presence of cellular debris .No abnormal cell or granuloma or hemoparasite seen. Correlate with biochemical markers of HLH.
7. ANCA and ENA profile – Negative

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation.

The pathophysiology of HLH is related to the failure to control the immune response that results in a hyper-inflammatory state and consequently to tissue destruction.[3] The dysregulation of the immune system is characterized by a persistent activation of Cytotoxic T lymphocytes , Natural Killers cells, and Macrophages.

HLH is characterized by the inability to clear the viral antigenic stimulus, resulting in the persistence

Volume 6, Issue 6; November-December 2023; Page No 94-99

and amplification of the immune response. Proinflammatory cytokines released by the activated immune cells results in a high level of macrophage activation, which result in hemophagocytosis, tissue damage, organ failure, and the other inflammatory manifestations of the syndrome[4]

Patients with HLH have elevated levels of numerous proinflammatory cytokines, particularly interferon gamma (IFN- γ). High levels of INF-γ, results in macrophage activation and the subsequent increased production of other proinflammatory cytokines.

The persistent activation of macrophages, NK cells, and CTLs in patients with HLH leads to excessive cytokine production by all those cells, a phenomenon named cytokine storm, and is thought to be responsible for multiorgan failure and the high mortality of this syndrome.[6,7]

Patients should have a bone marrow aspirate and biopsy to evaluate the cause of cytopenias and/or detect hemophagocytosis.[8,9,10] Bone marrow specimens should also be cultured, and examined for infectious organisms and evidence of malignancy, and secondary or triggering causes. Variable cellularity and infiltration of the bone marrow by activated macrophages is consistent with HLH.

Conclusion

The case report highlights the importance of raising a high index of suspicion for HLH in patients with vague etiology for multi-organ failure in post covid-19 cases. Additionally, to emphasize the seriousness of a history of COVID-19 infection and associated cytokine storm & HLH . Raised level of ferritin, Bone marrow biopsy, splenomegaly, hypofibrinogen, hypertriglyceridemia and pancytopenia, our patient fulfilled more than five out of eight criteria which are necessary for the diagnosis of HLH.

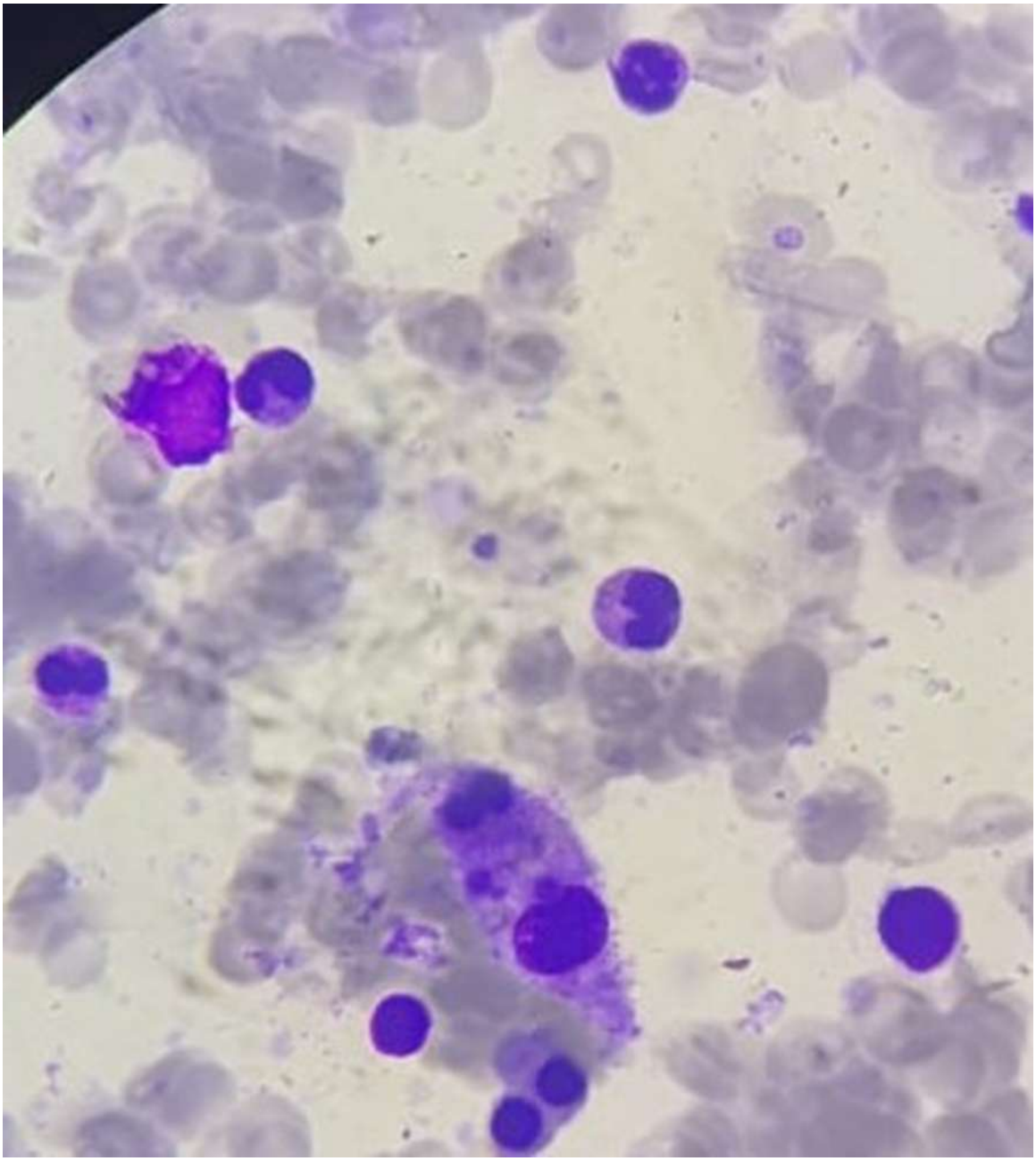
A routine screening of COVID-19 patients for secondary HLH is advised in patients which are at risk of developing shock, other systemic comorbidities or multi-organs failure. A well planned therapeutic approach comprising corticosteroids and immunomodulators may reduce the cytokine storm effects, and potentially reduce mortality.

References

1. Koumadoraki E et al: Hemophagocytic Lymphohistiocytosis and Infection: A Literature Review. Cureus. 2022 Feb 20;14(2):e22411.
2. Akenroye AT, Madan N, Mohammadi F, Leider J: Hemophagocytic lymphohistiocytosis mimics many common conditions: case series and review of literature. Eur Ann Allergy Clin Immunol. 2017, 49:31-41.
3. Soy M, Atagündüz P, Atagündüz I, Sucak GT : Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. Rheumatol Int. 2021 Jan;41(1):7-18.
4. Naous E et al : Hemophagocytic lymphohistiocytosis, a new cause of death during 'post-acute COVID-19 syndrome?' A case report. J Hematop. 2021 Apr 20;14(3):229-233.
5. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20.
6. Tiab M, Mechinaud F, Harousseau JL. Haemophagocytic syndrome associated with infections. Baillieres Best Pract Res Clin Haematol. 2000 Jun;13(2):163-78.
7. Ombrello MJ, Schulert GS. COVID-19 and cytokine storm syndrome: are there lessons from macrophage activation syndrome? Transl Res. 2021 Jun;232:1-12.
8. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into pathophysiology and practical guidelines. Biol Blood Marrow Transplant. 2010 Jan;16(1 Suppl):S82-9.
9. Lima R, Filho CC, Ferreira Filho CM, Vaisman M, Cossenza A, Rebello CP, Leite CA, de Oliveira Tavares D, Ramalho JF. Hemophagocytic syndrome and COVID-19. Respir Med Case Rep. 2020 Jul 10;31:101162.
10. Schnaubelt S, Tihanyi D, Strassl R, Schmidt R, Anders S, Laggner AN, Agis H, Domanovits H. Hemophagocytic lymphohistiocytosis in COVID-19: Case reports of a stepwise approach. Medicine (Baltimore). 2021 Mar 26;100(12):e25170.

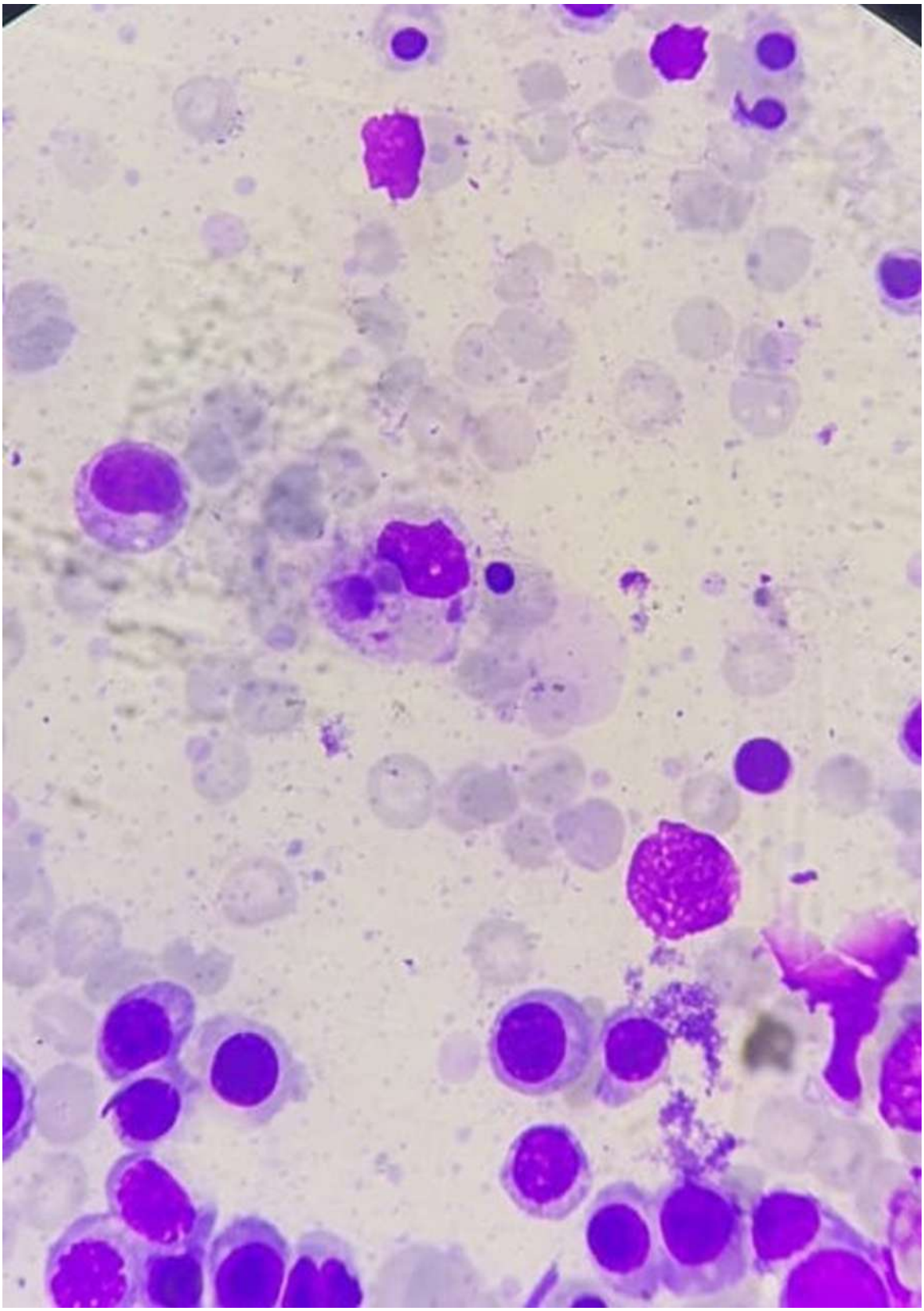
Figure 1 Bone Marrow Aspiration- Aparticulate and hemodilute showing prominence of histiocytes showing phagocytosis of RBCs and platelets .No abnormal cell or granuloma seen.

Volume 6, Issue 6; November-December 2023; Page No 94-99



Volume 6, Issue 6; November-December 2023; Page No 94-99

Figure 2 Bone Marrow Aspiration- Aparticulate and hemodilute showing prominence of histiocytes showing phagocytosis of RBCs.



Volume 6, Issue 6; November-December 2023; Page No 94-99