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Unmasking of systemic lupus erythematosus in a patient with hemophagocytic lymphohistiocytosis-macrophage activation syndrome (HLA-MAS) and diffuse alveolar hemorrhage

P. Sukhadiya[1], P. Kumar[1], D.S. Meena[1], A. Kumar P.H.[1], N. Vijayan[1], P. Garg[2], M.K. Garg[1]

[1]Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, India;
[2]Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur, India;

SUMMARY

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by macrophages and cytotoxic T cells with aberrant activation. The primary (genetic) form, which is caused by mutations that affect lymphocyte cytotoxicity and immune regulation, is most prevalent in children, whereas the secondary (acquired) form is prevalent in adults. Secondary HLH is commonly caused by infections or cancers, but it can also be caused by autoimmune disorders, in which case it is known as macrophage activation syndrome (MAS; or MAS-HLH).

A 25-year-old female presented with a high-grade fever that lasted for two weeks. His laboratory results revealed pancytopenia, neutropenia, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia. Based on the clinical presentation and laboratory findings, a provisional diagnosis of HLH has been made. A HLH protocol was utilized to treat the patient. During the course of hospitalization, systemic lupus erythematosus (SLE) was identified as the underlying cause. She improved dramatically after receiving an immunosuppressive regimen of etoposide, cyclosporine, and dexamethasone according to HLH protocol-2004 with individualized modifications.

The clinician should be aware that HLH may be the initial manifestation of underlying SLE. Early diagnosis and aggressive, individualized treatment are the key to improving outcomes.

Key words: *Hemophagocytic lymphohistiocytosis, systemic lupus erythematosus, ferritin, diffuse alveolar hemorrhage, pancytopenia.*

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome characterized by abnormal immune activation and tissue inflammation. The absence of normal downregulation of tissue macrophages leads to a cytokine storm and tissue damage (1). As seen in familial HLH, it can manifest as a single occurrence or as multiple episodes. HLH is triggered by any alteration in immune homeostasis. Viral infections (such as Epstein-Barr virus, EBV), hematological malignancies, and autoimmune diseases are the primary causes of secondary HLH. Among autoimmune diseases, juvenile idiopathic arthritis (JIA) and adult-onset Still's disease (AOSD) are frequent (up to 10% prevalence) macrophage activation syndrome (MAS; or MAS-HLH) causes (2). With a reported prevalence ranging from 0.9% to 10% in HLH cases, systemic lupus erythematosus (SLE) is emerging as an important etiology (3). We present the case of a young woman who was admitted to the hospital with pyrexia of unknown origin (PUO) and who later developed HLH and then SLE. Sometimes HLH can be the only initial symptom of underlying autoimmune diseases and this possibility should be evaluated.

Corresponding author:
Durga Shankar Meena
Department of Internal Medicine,
All India Institute of medical sciences,
Jodhpur, India
E-mail: dsmims14@gmail.com

CASE REPORT

We present the case of a 25-year-old woman who presented with a 15-day history of intermittent high-grade fever. She had no known comorbidities and was in her usual state of excellent health. The patient presented with a temperature of 39.5°C. The remaining vital signs were stable. The physical examination revealed mild splenomegaly; the remainder of the systemic examination was unremarkable. In light of the patient's leukopenia, ceftriaxone was administered due to the possibility of enteric fever. Simultaneous blood and urine cultures were sent. Later in her hospitalization, the patient developed pancytopenia and persistent high-grade fever (Table I). Infectious causes of febrile illness were ruled out because of sterile blood and urine cultures. Pancytopenia was evaluated via bone marrow biopsy, which revealed hypocellular bone marrow devoid of hematological malignancy. Except for hepatosplenomegaly and small mesenteric lymphadenopathy, chest and abdominal CT scans were unremarkable. Due to severe neutropenia (ANC 500), she was treated according to the protocol for febrile neutropenia (iv meropenem, antifungals). Her initial biochemical analysis revealed a significant increase in ferritin levels (Table I), prompting us to consider the possibility of HLH. She was suffering from fever, splenomegaly, pancytopenia, hyperferritinemia (3677 mg/dL), hypertriglyceridemia, and hypofi-

Table I - Hematological and biochemical indices during hospitalization.

Lab variables	Day 1 (on admission), (normal range)	Day 7	Day 14	Day 21	Day 28
Hemoglobin (g/dL)	10.2	8.7	6.8	9.1	10.7
Total leukocyte count (10^3/uL)	3.5 (4-11)	2.1	1.1	2.9	6.3
Platelets (10^3/uL)	170 (150-450)	89	56	112	189
LDH (IU/L)	532 (0-247)		2289	1270	
Ferritin (ng/mL)		256 (4-104)	3677	1245	245
Triglycerides (mg/dL)		156 (<150)	765	312	
Fibrinogen (mg/dL)		148 (180-350)	139	191	
CRP (mg/L)	4.1 (<1)	32		19	
Procalcitonin (ng/mL)	0.23 (<0.02)	0.12		0.21	
ALT/AST (IU/L)	122/187 (<35)	324/875	65/81	64/20	25/29
TP/albumin (mg/dL)	6.75/3.57	5.6/2.8	5.0/3.1	6.2/3.4	5.8/3.4
Total/direct bilirubin (mg/dL)	0.45/0.13	3.2/1.6	1.6/0.7	1.1/.4	0.5./0.2
Creatinine/BUN (mg/dL)	0.86/7		0.8/26	0.52/18	
Na/K (Meq/L)	136/4.3	129/4.4	118/3.7	126/3.9	136/4.1
24 hours urinary protein		935 mg (<150)			
ANA (IFA)			1:320		
Anti-ds-DNA antibodies		negative			positive
C3/C4		low			
CSF analysis	50 cells/mm^3, lymphomononuclear (80%), protein 59 (20-40), glucose 78 (40-70), CB NAAT: negative, ADA: 6 (<9), fungal and bacterial culture: sterile				
PBF/reticulocyte count	Normocytic, normochromic, few microcytes and pencil cells, no evidence of abnormal cells (reticulocyte count: 0.31%)				
Urine microscopy	5-10 RBCs, 2-4 pus cells, culture: sterile				

LDH, lactate dehydrogenase; CRP, C reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; BUN, blood urea nitrogen; ANA, antinuclear antibodies; IFA, immunofluorescence assay; PBF, peripheral blood film.

brinogenemia (Table I). There was no evidence of hemophagocytosis in her bone marrow and the CD-25 assay was unavailable at our facility. Nonetheless, she met 5 out of 8 HLH criteria (HLH 2004) (4). In addition, she exhibited hyponatremia, hypoalbuminemia, and transaminitis (Table I), supporting the diagnosis of HLH.

The patient begun treatment with the HLH 2004 protocol, which includes dexamethasone and etoposide. She was evaluated further to determine the underlying cause of HLH, and infectious causes were ruled out (negative cultures, negative viral serology for HIV, HBs Ag, anti-hepatitis C virus, EBV, cytomegalovirus and parvovirus). Despite the presence of yeast cells in her bone marrow culture, invasive candidiasis was unlikely due to a low candida score, absence of predisposing factors, and negative beta-D-glucan. We investigated further the other causes of HLH. No evidence of cancer was discovered. She did not exhibit any symptoms of an autoimmune disease (SLE or JIA) at the time of admission or in the past. Her anti-nuclear antibody (ANA; 1:320 dilution, speckled) was positive, but she did not meet SLE diagnostic criteria. On the 10th day of her hospitalization, she manifested neuropsychiatric symptoms including aggressive behavior, abnormal talking, and generalized tonic-clonic seizures. The following day, she developed malar rashes that persisted for several weeks. Additionally, her direct Coombs test (DCT) was positive and lactate dehydrogenase enzyme (2289) was elevated. A 24-hour urine test revealed 935 mg of proteinuria. The cytology and cultures of the cerebrospinal fluid were unremarkable. Initially, we attempted to classify central nervous system (CNS) symptoms as a spectrum of neurological HLH symptoms. However, the patient has already demonstrated a positive hematological response to an HLH induction regimen, making this an unlikely cause. The patient was identified as having SLE with a neurological flare, with an SLE-ACR/EULAR (2019) score of 21 and an SLEDAI of 25. Due to possible CNS manifestations of SLE and HLH, cyclosporin was added to the induction protocol. During hospitalization (on the 16th day after admission), the patient developed acute shortness of breath with hemoptysis. On auscultation, there

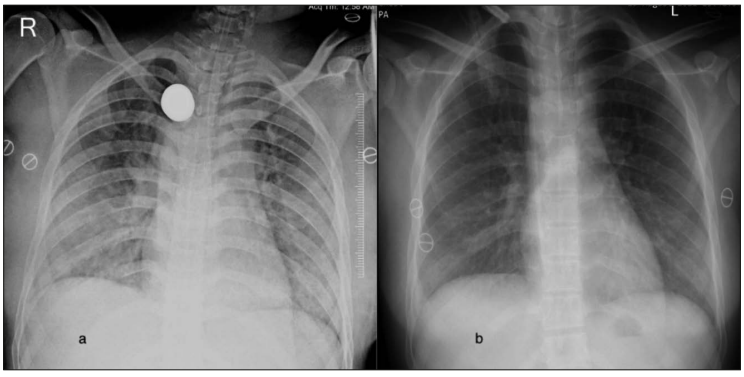

Figure 1 - A chest x-ray reveals bilateral diffuse infiltrates (a) that resolved following immunosuppressants and plasma exchange therapy for one week (b).

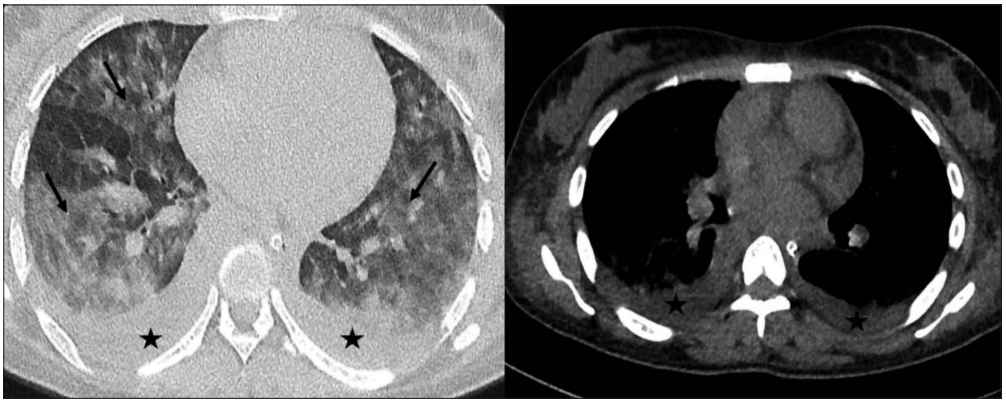

Figure 2 - Multifocal patchy ground glass opacity (black arrow) and bilateral pleural effusion (asterisk) suggestive of diffuse alveolar hemorrhage on computed tomography of the chest.

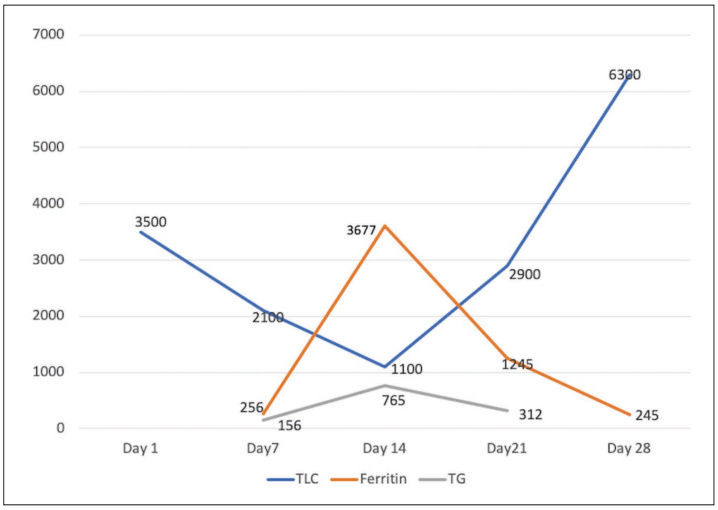

Figure 3 - The progression of ferritin, TG, and total leukocyte counts (TLC) during hospitalization.

were bilateral diffuse crepitations, and the chest x-ray revealed bilateral diffuse infiltrates (Figure 1A). Serial complete hemograms demonstrated an acute decrease in hemoglobin levels, and HRCT of the thorax suggested the presence of diffuse alveolar hemorrhage (Figure 2). Infections and acute pulmonary edema were ruled out (normal echocardiogram and cardiac enzymes). The patient was treated with three plasmapheresis cycles. She demonstrated remarkable radiological and clinical improvement (Figure 1B).

Over the next four weeks, her hematological and inflammatory parameters improved, indicating a recovery (Table I, Figure 3). In HLH-MAS, the optimal regimen has not been determined; therefore, based on clinical improvement and adverse events, we individualized the regimen in the continuation phase after eight weeks (etoposide, 75 mg/m^2 once a month, pulse dexamethasone every two weeks, and cyclosporin 6 mg/kg in two divided doses). At the three-month follow-up, she was doing well with no clinical or hematological signs of relapse.

DISCUSSION AND CONCLUSIONS

This patient presented with two weeks of febrile illness and subsequent cytopenia. She was initially evaluated in terms of PUO. She developed psychosis, seizures, and respiratory distress in the follow-up. Included in the differential diagnosis were infections, malignancies, and autoimmune diseases. The likelihood of an infectious etiology was high in the differential diagnosis, and a complete workup was performed, being negative. Regardless, a bone marrow biopsy revealed candida parapsilosis; however, her blood cultures were repeatedly negative, and we did not find any additional evidence of disseminated candidiasis. Five out of eight clinical/laboratory diagnostic criteria for HLH were met by the patient, including fever, pancytopenia, hypofibrinogenemia, splenomegaly, and hyperferritinemia.

HLH is typically considered a disease of the pediatric population, affecting infants predominately (5). It is diagnosed in an increasing number of adults up to the age of 65. MAS is used to describe HLH in the context of rheumatological disease, with the majority of evidence pertaining to patients with JIA. HLH can arise at any point during the progression of rheumatological disease (onset, during treatment); however, it is difficult to identify the underlying autoimmune disease when it is the initial or only manifestation. In addition, the presence of HLH may delay the diagnosis of underlying SLE. The diagnosis of HLH secondary to SLE is complicated due to the shared hematological (cytopenia) and neurological (symptoms) manifestations. In

situations where HLH is suspected, it is crucial to perform immunologic testing for SLE and avoid diagnostic delay. This may be significant because the prognosis and recurrence of HLH depend on the underlying cause. In such circumstances, serial ferritin levels are essential, as a mild increase in ferritin may be associated with a variety of inflammatory diseases. However, ferritin levels greater than 10,000 ng/mL have a specificity of approximately 97 percent and are rarely observed in conditions other than hemochromatosis and acute liver failure (6). Normal serum ferritin levels do not exclude the possibility of HLH (6), as our initial ferritin levels of 256 mg/dL demonstrate. Likewise, a rapid decline in ferritin levels correlates with improved outcomes (7).

Our patient also developed neurological and respiratory complications related to HLH-MAS in this instance. CNS manifestations typically occur in 30-70% of cases and are indicative of a poor prognosis (8, 9). Seizures are the most common manifestation of encephalopathy, followed by abnormal behavior, cranial nerve palsy, and other focal deficits (8). CSF abnormalities include pleocytosis (observed in 10 to 40% of patients) and elevated protein levels, which indicate a poor prognosis (10). In this instance, the CSF analysis revealed no abnormalities. In addition, the absence of hemophagocytosis in the bone marrow was a noteworthy finding. Hemophagocytosis is neither essential nor pathognomonic for the diagnosis of HLH. Hemophagocytosis occurrence is highly variable (25 to 100%). It may be absent during the initial stages of the disease (11). HLH is also characterized by hypotension, acute respiratory distress syndrome, hyponatremia (due to SIADH), and coagulopathy. Our patient developed diffuse alveolar hemorrhage, a symptom shared by HLH and SLE.

The treatment of HLH-MAS should be individualized based on clinical response, likelihood of relapse, and risk of chemotherapy-related adverse effects. The HLH-2004 protocol was utilized to treat this patient (4). The essential components of the intensive phase are etoposide and dexamethasone. Early use of cyclosporine (within the first eight weeks) was discouraged in HLH 2004 (4) due to a lack of key evidence and a high propensity to cause PRES (12). Our patient's neurological condition worsened despite receiving etoposide and dexamethasone; in this situation, guidelines (4) recommend intrathecal methotrexate. The patient's severe thrombocytopenia (platelet counts 20,000) precluded intrathecal administration. Thus, cyclosporine was added and continued at the end of the first week. Around the 6th week of taking immunosuppressants, she developed pancytopenia. However, she remained clinically asymptomatic (with normal ferritin levels), ruling out a relapse. Subsequently, the dosage and frequency of etoposide were reduced, and hematological parameters returned to normal.

This report highlights the fact that HLH can be the initial manifestation of underlying autoimmune disorders. The key to improving survival is early detection and aggressive immunosuppressants. In addition, the therapeutic regimen should be tailored to the patient's clinical response, underlying trigger, comorbidities, and risk of adverse effects.

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All authors contributed to the conception and design of the study. PS, DSM, and PK drafted the manuscript and contributed to the search for relevant literature. PG and AK performed a radio imaging analysis. MKG supervised the work and made suggestions to enhance the manuscript's design. The final manuscript has been read and approved by all authors.

Conflict of interest
The authors declare no potential conflict of interest.

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient has given written consent for disclosure of her personal and clinical information. The authors attest that they have collected all necessary patient consent forms. The patient has granted permission for images and other clinical data to be published in the journal on the consent form. The patient is aware that her name and initials will not be published, and that all reasonable efforts will be made to conceal her identity.

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