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ACUTE RESPIRATORY DISTRESS SYNDROME AS AN INITIAL PRESENTATION OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Abstract

A multisystem illness called hemophagocytic lymphohistiocytosis (HLH) is characterized by immune system dysregulation, hypercytokinemia, and hyperinflammation. This hyper-inflammation if caused by excessive macrophage activation. SLE (Systemic Lupus Erythematosus) is a chronic multi-system autoimmune disease which is caused by loss of tolerance to nuclear self-antigens in addition to the damaging autoantibodies formation. This is a rare case report of a young female known case of SLE who developed acute respiratory distress syndrome as an initial representation of the HLH.

Keywords: Hemophagocytic lymphohistiocytosis, Acute Respiratory Distress Syndrome (ARDS), Systemic lupus erythematosus, Macrophage Activation Syndrome.

INTRODUCTION

HLH is a multisystem disorder characterized by immune system dysregulation with hyperinflammation and hypercytokinemia. It is a rare s well as aggressive immune disorder characterized by the uncontrolled activation of T-lymphocytes as well as macrophages, leading to excessive cytokine production and systemic inflammation. When coupled with ARDS, a severe lung condition characterized by rapid onset of respiratory failure, the clinical picture becomes even more challenging.

It could be primary or secondary.[1] While secondary HLH is more frequent in adults, primary HLH is more common in children.2 Prolonged fever, pancytopenia, hepatosplenomegaly, and increased liver enzyme, lipid, and ferritin levels are typical signs of HLH. Rheumatic diseases are a common cause of secondary HLH. SLE as a cause of HLH is rare.[3.] Secondary HLH often arises as a complication of many underlying conditions like malignancies, infections, autoimmune diseases, or immunodeficiencies. The dysregulated immune response seen in HLH can precipitate ARDS, further complicating the clinical course and exacerbating respiratory compromise.

Early recognition of the signs and symptoms of secondary HLH and ARDS is crucial for prompt diagnosis and initiation of appropriate treatment strategies. Clinical manifestations may include fever, cytopenias, hepatosplenomegaly, and respiratory distress. Diagnostic evaluation typically involves a combination of laboratory tests, imaging studies, and sometimes invasive procedures such as bone marrow biopsy. Treatment of secondary HLH with concurrent ARDS necessitates a multi-disciplinary

approach involving specialists in hematology, critical care, infectious diseases, and respiratory medicine. Therapeutic interventions may include immunosuppressive agents to dampen the hyperactive immune response, supportive care to address respiratory compromise, and targeted treatment of underlying triggers. Overall, secondary HLH presenting with ARDS poses significant diagnostic and therapeutic challenges, emphasizing the importance of a coordinated and comprehensive approach to optimize patient outcomes. Early recognition, aggressive management, and close monitoring are essential pillars in the management of this complex clinical entity. Only a small number of instances of acute respiratory distress syndrome (ARDS), an uncommon and potentially fatal manifestation of HLH, have been documented in the literature so far. A young female patient with SLE who had severe respiratory distress due to subsequent hemophagocytic lymphohistiocytosis is the subject of this unusual case report.

Case Presentation

A 38y/o female, who has been diagnosed with SLE 4 years ago and had discontinued her medication for the past 2 years, came to the OPD with complaints of high-grade fever associated with generalized myalgia and breathlessness on exertion. She also gave a history of a rash over the cheek and bridge of the nose with oral painful ulcers for 15 days.

On examination, she was tachypnoic, malar rash and the Oral thrush were present, she was febrile with a pulse rate was 116/min and 98% on 4 liters oxygen by mask and her temperature was 101 degrees Fahrenheit. Per abdomen examination revealed hepatosplenomegaly. Lung auscultation revealed bilateral diffuse wheeze. Initially, her symptoms were attributed to an SLE flare, and planned to start on hydroxychloroquine and steroids after rheumatologist opinion.

At the time of admission, the patient's laboratory tests (Table 1) revealed pancytopenia.

ESR - 72 and CRP-22, Potassium-2.7, and a normal renal function test with low C3 levels. ECG suggestive of Sinus Tachycardia, Low voltage QRS, T wave inversion in V1-V4, II, III, aVf, left axis deviation, chest X-ray suggestive of cardiomegaly with minimal pericardial effusion. HRCT thorax showed subsegmental collapse of left anteromedial basal segment with mild volume loss in left lower lobe with right minimal pleural effusion and mild pericardial effusion.2D ECHO showed minimal pericardial effusion with EF 62%.

She was started on empirical intravenous antibiotics, nebulization, antifungals, a tablet of HCQ 200 mg once a day, oral steroids, and other supportive measures. She was started on intravenous potassium chloride for hypokalemia and electrolytes were monitored.

Tests for tropical infections urine routine and cultures were negative.

Two days after admission, she developed acute respiratory distress requiring Noninvasive ventilation & was transferred to the ICU. She eventually required intubation in view of worsening respiratory distress. A repeat X-ray of the Chest showed bilateral lung parenchymal infiltrates (Fig-1) and Based on the Berlin criterion (diffuse bilateral lung infiltrates and poor P/F ratio), she was diagnosed with ARDS. The high fever without an infection focus raised strong suspicions of HLH.

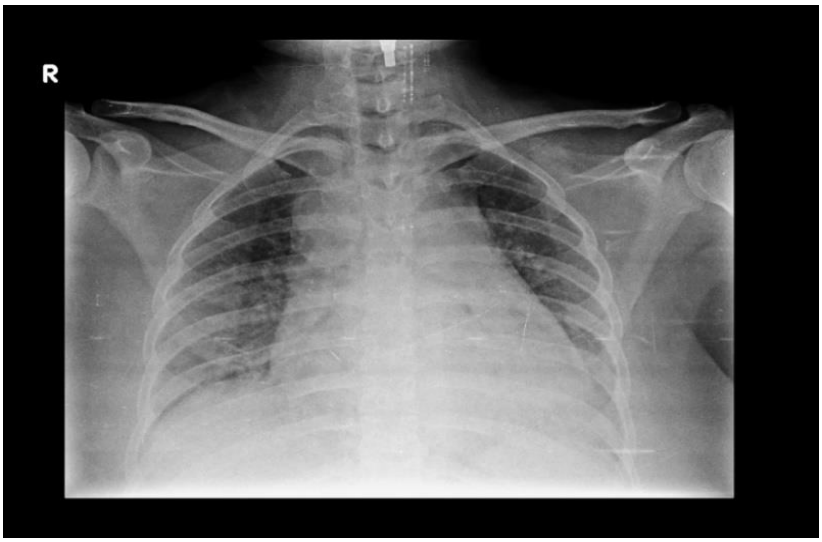

Figure 1: Bilateral lung infiltrates observed on chest X-ray

Further Laboratory tests (Table-1) revealed hyperferritinemia, hypertriglyceridemia, anaemia, thrombocytopenia, and hypofibrinogenemia. Peripheral blood smear results revealed a dimorphic blood picture with moderate leucopenia, thrombocytopenia, and red blood cell fragmentation consistent with HLH according to 2004 criteria. She was planned for bone marrow biopsy but she developed hypotension and started on inotropes and all supportive measures. Despite maximum inotrope support and other measures hypotension persisted and the patient went into asystole and was resuscitated according to ACLS protocol but could not be revived despite best efforts and succumbed to her illness.

Table 1: Lab investigation and its value

Lab Investigation	Value
HB	8.3 (12-15g/dl)
Total leukocyte count	2100 (4000-10000 cells/cumm)
Platelets	1.33 (1.5-4.5 lakhs/cu mm)
RFT	WNL
SGOT	110(14-36IU/L)
SGPT	51(5-50 IU/L)
Albumin	2.7(3.5-5gm/dl)
Potassium	3.3(3.5-5 Meq/L)
Urine spot PCR	0.583(<1)
ESR	72 (<19mm/hr)
CRP	22(<10mg/L)
C3	<40(88-165mg/dl)
C4	12.8(14-44mg/dl)
Serum ferritin	>1000(6.24-137ng/ml)
Serum LDH	1260(120-246 U/L)
Serum fibrinogen	231mg/dl
Serum triglycerides	304(<150mg/dl)
D-dimer	1650ng/ml
Dct	Positive

DISCUSSION

A severe and sometimes lethal illness known as HLH is characterized by immunological activation that results in multi-organ failure. It can also develop as a side effect of autoimmune diseases, cancer, infections, and immunosuppressive therapies[2]. Secondary or acquired HLH, which is frequently observed in adults, can result from a number of infectious diseases (like EBV, CMV, HIV, and tuberculosis), cancers (like leukaemia and lymphoma), autoimmune diseases (like SLE, and MS), and malignancies (like lymphoma and lymphoma). All of these illnesses cause severe phagocytic activation and compromised immune regulation[5].

In addition to the development of harmful autoantibodies, loss of tolerance to the nuclear self-antigens results in SLE illness. [6] Any organ may be affected by SLE, with symptoms varying from moderate to severe to potentially fatal. Constitutional symptoms, cutaneous lesions such as photosensitivity, musculoskeletal, malar rash, alopecia, mouth ulcers, renal, hematologic affliction, and neuropsychiatric are all included in the broad systemic affection.[7]

The medical literature reports MAS related to SLE, with an estimated 0.9–9% overall prevalence. In 46% of SLE patients, MAS manifests at the start of the first SLE flare; positive anti-DNA antibodies (63%) and hypocomplementaemia (56%) are prevalent in these patients.[8] In a large retrospective study, patients with SLE who were admitted to the hospital with a fever were given the 2016 sJIA PRINTO Classification Criteria for MAS. Of these patients, 1/3 have been classified as having MAS, and of those, 35% died, than to 3percent without MAS. This suggests that the classification criteria could be utilized to identify MAS in patients with fever & SLE, thereby facilitating effective treatment.[9]

The HLH-2004 protocol, which uses etoposide, dexamethasone, and cyclosporine with or without intrathecal methotrexate which has been followed by transplantation of hematopoietic stem cells, has become the standard of care for treating primary HLH.[10] Although secondary HLH treatment is not as well standardized, the main goal is still to address the underlying illness. Steroids, intravenous γ-globulin, cytotoxic drugs such as those in HLH-2004, or targeted immune treatment have all been tried if failed. Corticosteroids and immunosuppressive medications, such as cyclosporine, cyclophosphamide, intravenous immunoglobulin, and etoposide, have been used with varying degrees of efficacy in treating HLH caused by SLE.[11]

For MAS in SLE patients to be effectively treated, early identification, removal of triggering factors, and early immunosuppression are crucial.[12]

An uncommon and sometimes fatal consequence of certain autoimmune and inflammatory diseases, MAS is defined by the unchecked proliferation & activation of macrophages, which are responsible for engulfing and eliminating infections.

The MAS hallmark is an overwhelming and dysregulated immune response. A wide range of symptoms, including high fever, hepatosplenomegaly (enlargement of the liver and spleen), cytopenias (reduced blood cell counts), and dysfunction are caused by this, which leads to the release of excessive levels of proinflammatory cytokines, particularly interleukin-6 (IL-6).

Diagnosing MAS can be challenging because its symptoms overlap with those of the underlying autoimmune disease. Laboratory tests might show low platelet as well as WBC counts, elevated liver enzymes, and abnormalities in coagulation. Treatment

typically involves aggressive immunosuppression using corticosteroids and other immunomodulating medications like interleukin-1 (IL-1) inhibitors. In severe cases, patients may require intensive care, including interventions such as hemodynamic support and mechanical ventilation. Management of ARDS typically involves supportive care, including mechanical ventilation to assist with breathing and maintain oxygen levels. Treatment may also address the underlying cause, such as antibiotics for infections or addressing trauma-related issues.

The outcome of ARDS can vary widely, and the condition carries a significant risk of mortality, especially in severe cases. Early diagnosis and appropriate management in an intensive care setting are crucial for improving a patient's chances of recovery.

Patients suffering from SLE who have pancytopenia and a continuous fever should have MAS considered in their differential diagnosis. When relevant clinical signs and evidence are present, doctors should be extremely cautious when diagnosing MAS.

The high death rate must be avoided by receiving appropriate therapy as soon as possible. The most crucial markers for distinguishing between MAS and SLE flare-ups are thought to be hyperferritinemia and hypertriglyceridemia, not renal problems, anti-dsDNA antibody high titer, or complement levels. (sHLH) presenting with ARDS is a complex as well as potentially life-threatening condition which requires prompt recognition & intervention. This discussion will cover the pathophysiology, clinical presentation, diagnosis, and management strategies for this condition. HLH is a hyperinflammatory syndrome characterized by the immune system's uncontrolled activation, leading to excessive cytokine release and widespread tissue damage. In sHLH, this dysregulated immune response is triggered by underlying conditions such as infections, malignancies, autoimmune disorders, or immunodeficiencies. The exact mechanisms underlying the development of ARDS in the setting of sHLH are not fully understood. However, it is thought that the systemic inflammation and cytokine storm associated with HLH can directly injure the pulmonary endothelium and alveolar epithelium, leading to increased vascular permeability, pulmonary edema, and impaired gas exchange characteristic of ARDS.

Patients with sHLH may present with nonspecific symptoms such as fever, cytopenias, hepatosplenomegaly, and neurologic abnormalities. The development of ARDS further complicates the clinical picture, with patients typically exhibiting severe dyspnea, tachypnea, hypoxemia, and diffuse bilateral pulmonary infiltrates on imaging studies.

The sHLH diagnosis needs a higher index of suspicion along with a comprehensive evaluation to identify underlying triggers and associated complications such as ARDS. Diagnostic criteria for HLH involve the existence of specific clinical & laboratory findings, such as persistent fever, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis on bone marrow or tissue biopsy, and increased levels of soluble interleukin-2 receptor (sIL-2R) or ferritin. In patients presenting with ARDS and suspected sHLH, additional investigations may include imaging studies (chest X-ray, CT scan), blood cultures, viral serologies, autoimmune markers, and bone marrow biopsy to assess for evidence of hemophagocytosis and underlying etiologies. Management of sHLH with ARDS involves addressing the underlying trigger while providing supportive care and immunosuppression to control the hyperinflammatory response. Prompt initiation of treatment is essential to prevent further organ damage and improve outcomes. Supportive measures for ARDS include

supplemental oxygen, mechanical ventilation, and hemodynamic support as needed. Immunomodulatory therapy is aimed at suppressing excessive immune activation and may include corticosteroids, intravenous immunoglobulin (IVIG), and immunosuppressive agents such as etoposide or cyclosporine.

Additionally, targeted treatment of the underlying trigger, such as antimicrobial therapy for infections or chemotherapy for malignancies, is crucial for controlling the inflammatory cascade and achieving disease remission. In severe cases, refractory to standard therapies, consideration may be given to more aggressive interventions such as cytokine blockade (e.g., anti-interleukin-1 or anti-interleukin-6 agents) or hematopoietic stem cell transplantation for eligible patients. In summary, this case highlights an uncommon HLH with ARDS presentation. It is currently unknown how often adults with HLH really experience ARDS. Therefore, when a patient presents with acute respiratory failure and does not react well to suitable antimicrobial treatment, it is crucial to maintain HLH in the differential diagnosis.

CONCLUSIONS

HLH is a multisystem disorder marked by hypercytokinemia, hyperinflammation, and deregulation of the immune system. In addition to the development of harmful autoantibodies, loss of tolerance to nuclear self-antigens is the cause of SLE, a chronic multi-system autoimmune illness. In summary, secondary HLH presenting with acute respiratory distress syndrome is a challenging clinical syndrome related to significant mortality as well as morbidity. Timely recognition, thorough diagnostic evaluation, and multidisciplinary management are essential for optimizing outcomes in affected patients. Further research is needed to elucidate the underlying pathophysiology and identify more effective treatment strategies for this complex and often life-threatening condition. It is imperative to treat this illness as soon as possible in order to avoid potentially fatal organ failure. Rheumatological illnesses, autoimmune diseases, and hyperferritinemia are also associated with HLH. In this uncommon case study, a young male SLE patient first presented with acute respiratory distress syndrome and developed HLH highlighting the importance of considering HLH in patients with autoimmune conditions presenting with ARDS if all the laboratory investigations for other infections are found to be negative.

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