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Article

Hemophagocytic Lymphohistiocytosis Secondary to Macrophage Activation Syndrome in Adult-Onset Still's Disease: A Diagnostic and Therapeutic Challenge

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Abstract: Hemophagocytic Lymphohistiocytosis (HLH) is a rare and serious syndrome characterized by excessive inflammation and tissue damage due to abnormal immune activation. It presents in two main forms: a genetic variant predominantly affecting children, and an acquired form more common in adults, often secondary to infections, malignancies, or autoimmune diseases such as systemic lupus erythematosus (SLE). Macrophage Activation Syndrome (MAS), a subtype of HLH, frequently complicates rheumatologic conditions like systemic juvenile idiopathic arthritis (SJIA) and SLE. It is marked by intense inflammation driven by biomarkers such as interleukin (IL)-18 and IFN-γ. Clinical manifestations of HLH include persistent fever, enlargement of liver and spleen, blood cell deficiencies, elevated ferritin and triglyceride levels, abnormal liver function tests, decreased fibrinogen, and neurological symptoms, posing challenges in differential diagnosis. Diagnostic evaluation typically reveals blood cell deficiencies, elevated triglycerides, decreased fibrinogen, elevated ferritin, impaired natural killer cell function, and increased soluble IL-2 receptor levels. Early recognition and prompt intervention are crucial for improving outcomes in HLH and MAS. Diagnostic criteria incorporate clinical findings and laboratory parameters, supported by scoring systems such as HLH-2004 and HScore. Treatment strategies focus on limiting exposure to harmful agents and targeting specific cytokines like interferon gamma, IL-1, IL-18, and IL-6. Emerging therapies include corticosteroids, cyclosporine, anakinra, and, in severe cases, etoposide, showing promise in managing cytokine-release syndrome post-CAR T cell therapy. Adherence to standardized management protocols and evidence-based guidelines post-stem cell transplantation and CAR T cell therapy is essential for improving patient outcomes, including reduced mortality rates and faster resolution of inflammatory markers. This summary offers a comprehensive overview of HLH and MAS, highlighting diagnostic complexities, therapeutic approaches, and advancements in treatment aimed at enhancing patient care and prognosis.

Keywords: Hemophagocytic Lymphohistiocytosis (HLH); Macrophage Activation Syndrome (MAS); Adult-Onset Still's Disease (AOSD); Cytokine Storm; Immunosuppressive Therapy

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome caused by dysregulated immune activation, leading to excessive inflammation and tissue damage. It exists in two main forms: a primary genetic type, typically seen in children, and a secondary acquired form more common in adults, often triggered by infections, malignancies, or autoimmune conditions such as systemic lupus erythematosus (SLE) [1–3].

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Macrophage Activation Syndrome (MAS) is a subtype of HLH associated with rheumatologic conditions like systemic juvenile idiopathic arthritis (SJIA), adult-onset Still's disease (ASD), inflammatory myopathies, and SLE. It features a hyperinflammatory response with key biomarkers—especially interleukin-18 (IL-18) and interferon-gamma (IFN-γ)—that are useful for both diagnosis and prognosis [4,5].

Clinically, HLH presents with persistent high fever, hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, elevated transaminases, hypofibrinogenemia, and occasionally neurological involvement [6]. Due to symptom overlap with other diseases, diagnosis can be challenging. Laboratory findings typically include cytopenia, hypertriglyceridemia, low fibrinogen, elevated ferritin, impaired NK cell activity, and increased soluble IL-2 receptor levels [3]. Timely recognition and treatment are critical to improve prognosis [3,6,7].

Diagnosis relies on a combination of clinical features and lab parameters. For HLH, the HLH-2004 criteria include persistent fever, hepatosplenomegaly, cytopenia, coagulopathy, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia [8]. MAS, particularly in SJIA, is defined by hyperinflammation with markers such as high ferritin and low platelet count being especially significant [5,9]. In the context of CAR T cell therapy, HLH/MAS poses unique diagnostic challenges, and tailored criteria are required given its poor prognosis [10]. HScore and HLH-2004 remain widely used diagnostic tools [11].

Treatment aims to limit exposure to genotoxic agents like etoposide while modulating cytokine-driven inflammation. Recent data support the use of low-dose etoposide and cytokine-targeted therapies, including inhibitors of IFN-γ, IL-1, IL-6, and IL-18, for better clinical outcomes [12]. In CAR T cell-associated HLH/MAS, management typically includes high-dose corticosteroids, cyclosporine, anakinra, and in severe cases, etoposide, with IFN-γ blockade showing promise as a novel therapeutic approach [13]. However, there remains a pressing need for standardized diagnostic and therapeutic protocols, especially post–stem cell transplantation and CAR T cell therapy [14]. Adoption of evidence-based MAS-HLH management guidelines has significantly improved outcomes, including reduced mortality and faster resolution of inflammation [15].

Case Presentation:

This is the case of a 25-year-old woman with a complex medical history significant for adult-onset Still's disease (AOSD) with polyarthritis, heart failure with improved ejection fraction (HFimpEF); improved from 35% to 58%) secondary to non-ischemic cardiomyopathy (NICM) due to viral myocarditis, hypothyroidism, and a previous episode of macrophage activation syndrome (MAS). She presented to our facility with complaints of generalized weakness and worsening dyspnea, along with a productive cough. Notably, she had recently been hospitalized at an outside hospital for similar symptoms and had deteriorated post-discharge. One month prior, she was also admitted to our facility following a mechanical fall attributed to generalized weakness.

On presentation, the patient was febrile, hypotensive, and hypoxic. Laboratory evaluation revealed elevated lactic acid, liver function tests (LFTs), and thyroid-stimulating hormone (TSH). She was admitted to the medical intensive care unit (MICU), and broad-spectrum antibiotics and pulse-dose steroids were initiated. Rheumatology was consulted. A CT scan of the abdomen and pelvis showed gallbladder wall thickening with pericholecystic fluid, unchanged from prior imaging a year earlier. Abdominal ultrasound showed no gallstones but did reveal mild mural thickening. The patient showed clinical improvement after three days of high-dose steroids and antibiotics.

Given the findings of pancytopenia, transaminitis, and markedly elevated ferritin levels, there was concern for a possible flare of AOSD versus macrophage activation syndrome (MAS). A bone marrow biopsy from her earlier hospitalization revealed peripheral pancytopenia, hypocellular marrow (40%) with trilineage hematopoiesis, granulocytic hypoplasia, absence of iron storage without ringed sideroblasts, and scattered hemophagocytic histiocytes. Flow cytometry was negative for acute leukemia, lymphoproliferative disorders, and plasma cell neoplasms. These findings supported a diagnosis of hemophagocytic lymphohistiocytosis (HLH), likely secondary to AOSD. Past evaluations included a negative left axillary lymph node biopsy (for malignancy, lymphoproliferative disease, or Castleman disease) and an unremarkable blood flow cytometry

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report. General surgery was consulted to evaluate gallbladder inflammation as a potential infectious source. A HIDA scan suggested liver dysfunction or chronic cholecystitis without stones, and surgical intervention was deferred. Hepatology recommended ursodiol and outpatient follow-up with alkaline phosphatase isoenzyme assays. Due to persistent fever, rheumatology recommended continuing high-dose steroids.

The patient was discharged but subsequently presented to an outside emergency department with tachycardia, tachypnea, fever, hypotension, and respiratory distress, requiring bi-level positive airway pressure (BiPAP) support. She was admitted to their MICU for septic shock and tested positive for Influenza A. Chest CT revealed multifocal pneumonia but was negative for pulmonary embolism. Treatment was initiated with oseltamivir, vancomycin, meropenem, fluconazole, and hydrocortisone. Her hospital course was complicated by acute kidney injury (AKI) following vancomycin use, furosemide administration, and CT contrast exposure. Although creatinine normalized before transfer, vancomycin was discontinued. She received one unit of packed red blood cells (PRBC) for hemoglobin <7 g/dL. Sputum cultures grew *Pseudomonas aeruginosa*, and blood cultures were positive for methicillin-sensitive *Staphylococcus aureus* (MSSA). A transesophageal echocardiogram (TEE) was negative for endocarditis.

At her family's request, she was transferred back to our facility for continued care. On admission in early June, she continued to have severe neutropenia. Given her steroid requirement for AOSD, she was started on atovaquone for Pneumocystis jirovecii pneumonia (PJP) prophylaxis, as trimethoprim-sulfamethoxazole had previously caused a rash. Acyclovir and fluconazole were also initiated for infection prophylaxis. Her pulse-dose steroids were tapered, and she met HLH criteria based on the following: markedly elevated ferritin (37,850 ng/mL), elevated IL-2 receptor levels, triglycerides of 326 mg/dL, fever, mild splenomegaly, elevated LFTs, and supportive bone marrow biopsy findings. Hematology-oncology initiated an HLH protocol with dexamethasone at 10 mg BID starting early June, which was later tapered to 10 mg daily in mid-June and then to 5 mg daily after two weeks.

Despite downtrending bilirubin and AST/ALT levels, further autoimmune workup was recommended, including antimitochondrial and anti-smooth muscle antibodies, which were both negative. On day 5 of hospitalization, a liver biopsy was performed by interventional radiology, during which she received one unit of cryoprecipitate. That same day, a rapid response was called for hypotension (MAPs in the low 60s). An arterial blood gas revealed a lactate >10 mmol/L, hemoglobin of 4 g/dL, and pCO_2 of 19 mmHg. STAT labs showed potassium of 7.0 mEq/L, creatinine of 1.62 mg/dL, and lactate of 14.5 mmol/L. The massive transfusion protocol was initiated. The patient also complained of abdominal pain radiating to her back. A bedside FAST exam was concerning for hemoperitoneum, prompting emergent surgical exploration. General surgery evacuated 5 liters of hemoperitoneum and identified hepatomegaly, liver congestion, and a bleeding 2-cm laceration in the right liver lobe, which was repaired.

The patient was transferred to the surgical ICU (SICU) postoperatively. Due to extremely high peak airway pressures (90–100s) and ventilatory failure, she required veno-venous ECMO support for nine days. A second-look laparotomy was performed on hospital day 7 for wound vac removal and abdominal closure. The liver biopsy revealed features consistent with HLH, including CD68-positive histiocytes, 25% steatosis, 10% hepatocyte necrosis, bridging fibrosis, pericellular fibrosis, and mild portal inflammation, with no iron deposition or digested PAS staining. Cytokeratin-7 immunostaining showed ductular proliferation without hepatocyte metaplasia.

Ventilatory management included lung-protective strategies and inhaled epoprostenol (0.5 mg/vial). ECMO settings were titrated to maintain MAPs between 65–80 mmHg and SpO_2 >92%. The patient was decannulated in mid-June. She received micafungin for one week, vancomycin for six days, and meropenem for 12 days. Due to refractory AOSD/MAS and lack of prior response to anakinra, hematology-initiated etoposide therapy. Continuous veno-venous hemodialysis (CVVHD) was started on hospital day 12 due to AKI, with a net-negative fluid balance goal. Labs revealed a fibrinogen of 129 mg/dL and hemoglobin of 7.1 g/dL, prompting transfusion of PRBCs, platelets, and cryoprecipitate.

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Despite persistently negative cultures throughout the admission, the patient's profound neutropenia (ANC as low as 0.52 ×10⁹/L) necessitated a low threshold for empiric antibiotics. She received her first dose of etoposide in mid-June at a 50% dose reduction due to transaminitis, which was well tolerated. She was transferred back to the MICU and extubated to 4–5 L/min oxygen via nasal cannula. Her second reduced dose of etoposide was administered shortly thereafter. CVVHD was discontinued, and intermittent hemodialysis (IHD) began, with a successful 1 L ultrafiltration while maintaining normotension.

A mid-June sputum culture grew *Stenotrophomonas maltophilia*, susceptible to levofloxacin; TMP-SMX was avoided due to concern for myelosuppression. Inflammatory markers including procalcitonin and CRP declined during the hospitalization, despite persistent pancytopenia. Her third etoposide dose was given in late June, again at 50% dosing due to ANC of 0.03 ×10⁹/L, with ongoing clinical improvement. EBV PCR was <35 IU/mL, and although EBV DNA was detected, it was not quantifiable; thus, rituximab was not indicated. Filgrastim support was continued. On June 24th, after 10 days in the MICU and 13 days in the SICU, the patient was clinically stable and downgraded for ongoing care.

Discussion:

Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are hyperinflammatory syndromes characterized by excessive immune activation, leading to multiorgan dysfunction and high mortality if not promptly diagnosed and treated. While HLH can be primary (familial) or secondary to infections, malignancies, or autoimmune diseases, MAS is a subtype of secondary HLH typically associated with rheumatologic conditions.[16]

The pathogenesis of HLH/MAS involves uncontrolled activation of cytotoxic T lymphocytes and macrophages, resulting in a cytokine storm.[11] This hyperinflammatory state leads to clinical features such as persistent fever, hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, and coagulopathy. In MAS, these features are superimposed on underlying rheumatologic diseases, complicating the clinical picture. A case reported by Dilibe et al. described a 21-year-old female with systemic juvenile idiopathic arthritis (SJIA) who developed MAS, initially misdiagnosed as sepsis.[1] Prompt recognition and steroid therapy led to recovery, highlighting the importance of considering MAS in febrile patients with rheumatologic diseases.

Diagnosing HLH/MAS is challenging due to nonspecific symptoms and overlap with other conditions like sepsis. The HLH-2004 criteria and the HScore are commonly used diagnostic tools, but they have limitations, especially in adults. Emerging biomarkers, such as soluble IL-2 receptor (sCD25) and natural killer (NK) cell activity, may improve diagnostic accuracy .

Yaremenko et al. presented a case of HLH in an adult without a clear underlying cause, emphasizing the need for heightened clinical suspicion and comprehensive evaluation in patients with unexplained systemic inflammation. [6] Systemic lupus erythematosus (SLE) is a known trigger for secondary HLH/MAS. Sukhadiya et al. reported a case where HLH/MAS unmasked underlying SLE in a patient presenting with diffuse alveolar hemorrhage, underscoring the importance of considering autoimmune etiologies in HLH presentations .

Similarly, Ahmad et al. described a 29-year-old female who presented with HLH as the initial manifestation of SLE. [16]Treatment with dexamethasone, etoposide, and belimumab led to complete recovery, highlighting the role of targeted therapy in such cases.

HLH/MAS can occur as a complication of malignancies and their treatments. Chimeric antigen receptor (CAR) T-cell therapy, particularly with agents like tisagenlecleucel, has been associated with HLH/MAS.[10] Rainone et al. reported a case where interferon-γ blockade with emapalumab, along with anakinra and corticosteroids, successfully treated CAR T-cell therapy–associated HLH/MAS.[17]

A review by Sandler et al. emphasized the need for specific diagnostic criteria and management strategies for HLH/MAS following hematopoietic stem cell transplantation (HSCT) and CAR T-cell therapy, given the distinct pathophysiology and clinical course in these settings.[14]

Traditional HLH/MAS treatment regimens include high-dose corticosteroids and etoposide. However, concerns about toxicity have led to the exploration of targeted therapies. Schulert et al.

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discussed the use of cytokine-directed therapies, such as IL-1 inhibitors (anakinra), IL-6 inhibitors (tocilizumab), and interferon-γ blockers (emapalumab), which have shown promise in dampening hyperinflammation while minimizing adverse effects.[12][17] An evidence-based guideline implemented at a pediatric institution resulted in a significant reduction in mortality from 50% to 6% among HLH/MAS patients, demonstrating the impact of standardized, multidisciplinary approaches to management .[15]

Conclusions

This case highlights the diagnostic complexity of HLH secondary to MAS in a patient with adult-onset Still's disease (AOSD). The diagnosis was established based on persistent high-grade fever, hepatosplenomegaly, cytopenias, hyperferritinemia (>37,000 ng/mL), elevated sCD25, hypertriglyceridemia, and bone marrow evidence of hemophagocytosis—fulfilling at least five HLH-2004 diagnostic criteria. A thorough workup excluded other differential diagnoses such as infection, malignancy, and other autoimmune conditions. Prompt initiation of immunosuppressive therapy with high-dose corticosteroids and cyclosporine, along with supportive care, led to a marked clinical improvement. The patient responded well to treatment and was discharged in stable condition.

This case underscores the importance of early recognition and timely intervention in HLH/MAS, particularly in patients with underlying rheumatological conditions such as AOSD, to prevent fatal outcomes.

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