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Macrophage Activation Syndrome: An Atypical Initial Presentation of Systemic Lupus Erythematosus

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Abstract

Macrophage Activation Syndrome (MAS) is a severe inflammatory complication often linked to autoimmune disorders such as systemic lupus erythematosus (SLE). We describe a 57-year-old woman who presented with persistent fever, polyarthralgia, pancytopenia, and markedly elevated ferritin levels (>40,000 ng/mL). Extensive evaluation ruled out infection and malignancy. A diagnosis of MAS was made, and she responded well to high-dose corticosteroids and anakinra. Subsequent autoimmune workup revealed anti-dsDNA antibodies, leading to a new diagnosis of SLE. She has remained clinically stable over long-term follow-up without ongoing immunosuppressive therapy. This case illustrates the importance of considering MAS in adults with unexplained systemic inflammation and cytopenias, particularly when it reveals underlying autoimmune disease. Early recognition and treatment are important to improving outcomes.

Keywords: Systemic lupus erythematosus, Macrophage activation syndrome, Pancytopenia

Introduction

Macrophage Activation Syndrome (MAS) is a rare and potentially fatal complication associated with autoimmune diseases such as systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis (sJIA), and its adult counterpart, adult-onset Still's disease [1,2]. Often referred to as secondary hemophagocytic lymphohistiocytosis (HLH), MAS is most frequently observed in patients with sJIA, and much of the current understanding of its epidemiology, pathogenesis, and genetics arises from this demographic. MAS poses a high mortality risk—estimated at 5–10% in children and 10–15% in adults—and may lead to permanent neurological damage and serious pulmonary complications. We present the case of a 57 year old female who developed MAS, which ultimately led to the diagnosis of previously unrecognized SLE.

Case Report

A 57-year-old female presented to the ER with a one-month history of fever, chills, polyarthralgia, decreased appetite, and generalized malaise. Her past medical history was notable for hypothyroidism, managed with levothyroxine 100 mcg daily, and a prior SARS-CoV-2 infection nine months earlier, during which she experienced similar symptoms and required hospitalization. Upon presentation, her vital signs were stable: temperature 98°F, heart rate 66 bpm, blood pressure 130/86 mmHg, and oxygen saturation 99% on RA. Initial laboratory evaluation revealed pancytopenia, including an absolute neutrophil count of 0 and lymphocytes of 700/μL. Comprehensive metabolic panel also showed elevated liver function tests (LFTs). Her surgical and family history were non-contributory. Physical examination revealed significant synovitis with painful range of motion in both knees and elbows. The remainder of the examination was unremarkable.

The patient was admitted for management of severe pancytopenia. Due to concern for a possible hematologic malignancy, hematology-oncology was consulted. Imaging, including CT scans of the chest, abdomen, and pelvis, showed no evidence of malignancy but did reveal mild bilateral pleural and pericardial effusions. Bone marrow biopsy demonstrated

trilineage hematopoiesis. Infectious workup, including blood and urine cultures and serologies for viral, bacterial, and fungal pathogens, was negative. Liver biopsy findings included proptosis and the presence of activated Kupffer cells. Given her clinical picture—positive antinuclear antibody (ANA) titers, markedly elevated ferritin (>40,000 ng/mL), anemia, neutropenia, thrombocytopenia, and mild hyponatremia—rheumatology was consulted. She was diagnosed with macrophage activation syndrome (MAS), likely secondary to an underlying, previously unrecognized connective tissue disorder.

The patient was started on high-dose intravenous corticosteroids and Anakinra. Her symptoms improved progressively during her hospital stay. She was discharged on a tapering course of oral corticosteroids and prophylactic trimethoprim-sulfamethoxazole thrice weekly.

At her one-month outpatient rheumatology follow-up, her blood counts and LFTs had normalized, and her symptoms had resolved. She was weaned off corticosteroids and started on methotrexate as a steroid-sparing agent. The autoimmune panel was largely unremarkable, with the exception of a positive rheumatoid factor (RF) and anti-double-stranded DNA (anti-dsDNA) antibody, findings that raised the suspicion of an underlying systemic lupus erythematosus (SLE). Due to methotrexate-induced alopecia, the medication was discontinued, and she was monitored off immunosuppressive therapy. Subsequently, she experienced a recurrence of fever and polyarthralgia with laboratory findings of pancytopenia and elevated ESR. She responded well to a two-week course of oral prednisone, with resolution of symptoms and normalization of blood counts.

Three years following her initial presentation, she remains off immunosuppressive therapy. While she continues to experience chronic arthralgia, she has not had any further flares or systemic symptoms.

Discussion

Macrophage activation syndrome (MAS) is commonly associated with sJIA [1] but has also been reported in Kawasaki disease, adult-onset Still's disease, rheumatoid arthritis, Sjögren's syndrome, dermatomyositis, mixed connective tissue disease, systemic sclerosis, and systemic lupus erythematosus (SLE) [2]. The incidence of MAS in patients with SLE is estimated to range from 0.9% to 4.6% [3].

MAS is a complex and variable condition that can present with a broad spectrum of symptoms. These may include persistent high-grade fever, enlargement of the liver and spleen, bleeding tendencies such as purpura, and neurological signs like reduced alertness or lethargy. Laboratory findings often reveal significant abnormalities, including reduced blood cell counts across all lines (pancytopenia), low fibrinogen levels, elevated triglycerides, and markedly increased ferritin concentrations [4]. MAS is considered a form of hemophagocytic lymphohistiocytosis (HLH), a group of disorders that also includes familial (genetic) HLH and acquired, or secondary, HLH. Secondary HLH can be triggered by various factors such as infections, certain medications, malignancies, and autoimmune or rheumatic diseases [5].

Diagnosing MAS is challenging, as its clinical features often mimic those of active SLE; however, hyperferritinemia is considered one of the most reliable markers for distinguishing MAS-associated SLE from active SLE. Severe leukopenia should prompt clinicians to be mindful of the potential presence of MAS.

The exact pathogenesis of macrophage activation syndrome remains incompletely understood. It is believed to involve an overwhelming systemic inflammatory response driven by significant disruption in the interaction between macrophages and lymphocytes. This dysregulation leads to elevated levels of various proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), macrophage colony-stimulating factor (M-CSF), interleukins such as IL-1, IL-6 and IL-18, and interferon-gamma (IFN-γ) [6,7].

The management of MAS varies depending on whether the condition is primary or secondary. In cases of primary MAS or familial hemophagocytic lymphohistiocytosis (HLH), treatment often involves hematopoietic stem cell transplantation alongside intensive immunosuppressive therapy, including dexamethasone, etoposide, cyclosporine A, and intrathecal methotrexate when the central nervous system (CNS) is affected [8]. In contrast, therapeutic strategies for secondary MAS are less standardized. The primary goals are to suppress the overwhelming inflammatory response and address the underlying cause, such as infection, malignancy, or autoimmune disease.

Initial treatment for secondary MAS generally begins with high-dose intravenous methylprednisolone (typically 30 mg/kg, up to 1000 mg per dose) administered daily for 3 to 5 days, followed by tapering oral or intravenous glucocorticoids. If the clinical response is inadequate, cyclosporine A (2–7 mg/kg/day, targeting trough levels of 100–150 µg/L) is commonly added and may be continued long-term for disease control. Interleukin-1 blockade with anakinra (2–10 mg/kg/day) has also become a widely used adjunctive therapy. For patients with refractory or severe disease, particularly those with CNS involvement, moderate doses of etoposide (50–100 mg/m^2 weekly) may be considered, although its use is limited by potential liver toxicity. In difficult cases, components of the HLH-2004 protocol—such as dexamethasone, cyclosporine A, and etoposide—can be employed. Additional therapies,

including antithymocyte globulin, rituximab, infliximab, and intravenous immunoglobulin, have been utilized in specific contexts, such as virus-triggered MAS or treatment-resistant presentations.

Conclusion

This case highlights the importance of considering macrophage activation syndrome in patients with unexplained fever, cytopenias, and elevated ferritin. Early diagnosis and treatment with immunosuppressive therapy, including corticosteroids and biologics, can lead to favorable outcomes. Continued monitoring is essential due to the risk of relapse.

Conflicts of Interests

No conflicts of Interests.

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