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The Silent Hyperinflammatory Storm: Unmasking Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

Dr. Ankita Sachdev, Dr. Divin Kalappa , Dr. Yasha Dedhia, Dr. Mumtaz sharif
Junior Resident, Senior Resident, Senior Resident, Professor
Dr. D. Y. Patil University, School of Medicine, Nerul, Maharashtra, India

***Corresponding Author:**
Dr. Divin Kalappa
Senior Resident, Department of Paediatrics , DR DY Patil University,
School of Medicine, Nerul, Navi Mumbai, Maharashtra, India

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory disorder characterized by uncontrolled activation of macrophages and cytotoxic T lymphocytes. HLH can be primary or secondary, Macrophage activation syndrome (MAS) represents a form of secondary HLH, most commonly occurring in systemic juvenile idiopathic arthritis (sJIA). Although sJIA itself is uncommon, the development of MAS remains rare and continues to pose a significant diagnostic challenge. The clinical manifestations of HLH frequently overlap with active sJIA and severe infection, and established diagnostic criteria may not be fully met during the early or evolving stages of the disease, resulting in delayed recognition. Thus, early recognition of this rare condition, supported by systematic assessment of evolving clinical and laboratory patterns, is essential for prompt diagnosis and effective management. We report a case of Macrophage Activation Syndrome (MAS) secondary to systemic juvenile idiopathic arthritis in a 3-year-old child who had a one-year history of intermittent high-grade fever and progressively worsening chronic arthritis, ultimately resulting in an inability to walk

Keywords: NIL

Introduction

Macrophage activation syndrome (MAS) is a life-threatening hyperinflammatory condition belonging to the spectrum of secondary hemophagocytic lymphohistiocytosis (HLH).[1] It is characterized by dysregulated immune activation leading to excessive proliferation and activation of macrophages and cytotoxic T lymphocytes, resulting in widespread cytokine release with multisystem involvement. Clinically, MAS manifests with persistent high-grade fever, bicytopenias, coagulopathy, hepatic dysfunction, neurological involvement, and evidence of hemophagocytosis in bone marrow or other reticuloendothelial tissues.[2]

Macrophage activation syndrome (MAS) can occur in the setting of autoimmune systemic inflammatory diseases such as systemic juvenile idiopathic arthritis, whereas HLH more commonly develops in association with viral infections or underlying malignancies.[3] MAS has also been reported in association with other conditions including systemic lupus erythematosus, Kawasaki disease, dermatomyositis, sarcoidosis, and Sjögren's syndrome. Infectious triggers encompassing viral, bacterial, fungal, parasitic, and zoonotic pathogens are well-recognized precipitants of MAS.[4] Less commonly, MAS has been described in association with malignancies, particularly hematological cancers.

Drug-induced MAS has also been reported, with implicated agents including non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic

drugs such as methotrexate and sulfasalazine, gold salts, and biologic therapies targeting cytokine pathways, including tumor necrosis factor-α inhibitors (e.g., adalimumab) and interleukin-6 receptor antagonists (e.g., tocilizumab).[5] In view of its fulminant course and high mortality, timely recognition of MAS is

imperative, particularly in patients with underlying rheumatologic disease in whom clinical features may be indistinguishable from disease flares or sepsis.[6]

The diagnosis of HLH and MAS remains challenging due to their nonspecific and often atypical clinical presentation.[7] Symptoms frequently overlap with sepsis, malignancy, or multisystem inflammatory syndrome in children (MIS-C). Furthermore, diagnostic criteria may not be fulfilled early in the disease course, as laboratory abnormalities such as cytopenias, hyperferritinemia, hepatic dysfunction, and coagulopathy can evolve gradually.[8] Delayed recognition may adversely affect outcomes, highlighting the importance of maintaining a high index of suspicion.

Case Presentation

A 3-year-old female child presented to us with a one-year history of intermittent high grade fever and chronic arthritis. Arthritis was in right knee more than left associated with tenderness, pain, redness, warmth and manifested as difficulty in walking and gradually progressing to inability to stand without support due to significant pain. There was swelling over both wrists, which was generalized in nature. The swelling was non-tender, with no local rise of temperature or erythema. It was not associated with restriction or decrease in range of movements of the wrist joints.

Anthropometrically, the child falls under Severe Acute Malnutrition with an observed weight of 9.2 kg and height of 91 cm. On examination she had bilateral cervical lymph nodes measuring 2*1cm each and bilateral inguinal lymph nodes each measuring 4*2.5cm. She had received intermittent symptomatic treatment for arthritis with non-steroidal anti-inflammatory drugs for the past 1 year, with only transient relief.

During prior evaluations, rheumatologic work-up revealed negative rheumatoid factor, anti–cyclic citrullinated peptide antibodies. In view of chronic fever, joint involvement, presence of significant bilateral cervical and inguinal lymphadenopathy and severe acute malnutrition; systemic juvenile idiopathic arthritis, malignancy and haemophagocytosis histiolymphocytosis were initially considered as leading differential diagnoses.

On admission, laboratory investigations revealed severe microcytic hypochromic anemia with a hemoglobin of 7 g/dL, MCV-45 fL, MCH- 14.2 pg, MCHC- 31.6g/dL with a total leukocyte count of 13,800/mm³, and with a platelet count of 4.9 × 10^5/mm³. Inflammatory markers were markedly elevated, with an erythrocyte sedimentation rate of 32 mm/hour and a C-reactive protein level of 142 mg/L. Ultrasonography of both knees revealed well-defined heterogeneously hypoechoic collections involving the bilateral suprapatellar bursae with minimal liquefaction, associated with synovial thickening. Magnetic resonance imaging of both knees demonstrated diffuse synovial thickening with joint and suprapatellar effusion along with cartilage thinning, findings suggestive of an inflammatory/infective etiology. However, MRI did not provide a definitive etiological diagnosis. Clinically, the child fulfilled criteria consistent with systemic juvenile idiopathic arthritis, with quotidian fever persisting for more than two weeks, associated arthritis, and lymphadenopathy; nevertheless, infections and malignancy needed to be ruled out before establishing the diagnosis.

An extensive laboratory evaluation was performed to identify possible infectious, autoimmune, and inflammatory etiologies. Extended Widal testing for brucellosis, antinuclear antibody for underlying autoimmune disease, anti-tissue transglutaminase IgA to screen for celiac disease, and fecal calprotectin to assess for inflammatory bowel disease (IBD), all of which were negative. Hemoglobin electrophoresis was suggestive of β-thalassemia trait. CBNAAT for tuberculosis was done which was negative. Further evaluation revealed markedly elevated serum ferritin levels (19,468 ng/mL) and increased serum triglycerides (257 mg/dL), with a fibrinogen level of 296 mg/dL. The coagulation profile was normal, with an INR of 1.19 and normal bleeding time and clotting time. These findings were suggestive of Macrophage Activation Syndrome, likely secondary to systemic juvenile idiopathic arthritis.

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To exclude malignancy and confirm the underlying etiology, lymph node biopsy and bone marrow aspiration with biopsy were performed. Lymph node histopathology demonstrated reactive follicular hyperplasia with sinus histiocytosis and evidence of hemophagocytosis. Bone marrow aspiration and biopsy revealed erythroid hyperplasia with micronormoblastic maturation, consistent with iron deficiency anemia and β-thalassemia trait, along with prominent histiocytosis and hemophagocytosis. These findings collectively supported a diagnosis of macrophage activation syndrome secondary to systemic juvenile arthritis.

Once the diagnosis was established, the patient was treated with intravenous methylprednisolone at a dose of 30 mg/kg/day for three consecutive days, followed by oral prednisolone at 2 mg/kg/day. Subcutaneous methotrexate was initiated at a dose of 15 mg/m² weekly. The child showed significant clinical improvement, with marked reduction in bilateral knee swelling and pain, and regained the ability to walk independently.

Discussion

This case represented an atypical and diagnostically challenging presentation of systemic inflammation. The child had prolonged intermittent high-grade fever with chronic progressive arthritis and significant generalized lymphadenopathy, which initially raised strong suspicion for chronic infection, hematological malignancy, or other infiltrative disorders. Given the one-year duration of symptoms, persistent lymphadenopathy, severe anemia with leukocytosis and thrombocytosis, and sustained systemic inflammation, infection, malignancy, hematologic causes were prioritized and systematically excluded. MRI of the knees supported an inflammatory arthropathy but did not establish etiology. Therefore, tissue diagnosis was pursued. Lymph node biopsy demonstrated reactive hyperplasia with hemophagocytosis, and bone marrow aspiration and biopsy revealed prominent histiocytosis with hemophagocytosis, effectively excluding malignancy while supporting an underlying hemophagocytic process.

The chronic indolent course, absence of early-onset fulminant cytopenias, lack of central nervous system involvement, and absence of a suggestive family history argued against primary (familial) hemophagocytic lymphohistiocytosis. In contrast to classical HLH, which often presents with rapid clinical deterioration, our patient had a prolonged disease course spanning one year. Similar observations have been reported by Janka and Lehmberg, who highlighted that secondary HLH may exhibit a more heterogeneous and sometimes subacute presentation depending on the underlying trigger.[3]

The overall clinical phenotype was most consistent with systemic juvenile idiopathic arthritis (sJIA). Hyperferritinemia remains one of the most sensitive markers for MAS. In our patient, ferritin levels were markedly elevated (>19,000 ng/mL), which strongly supported the diagnosis. Ravelli et al. (2016) proposed classification criteria for MAS in sJIA, emphasizing ferritin >684 ng/mL along with any two ofthe following: platelet count <181 ×10⁹/L, AST >48 U/L, triglycerides >156 mg/dL, and fibrinogen <360 mg/dL.[2] In our patient, fever persisted for more than two weeks, ferritin was markedly elevated, triglycerides were raised, and fibrinogen met the diagnostic cut-off, fulfilling criteria for MAS.

The absence of profound cytopenias in our case contrasts with the HLH-2004 criteria described by Henter et al., where bicytopenia or pancytopenia is a key feature, highlighting that macrophage activation syndrome (MAS), although within the HLH spectrum, has distinct clinical and laboratory characteristics. [1] Studies by Grom and Mellins have similarly noted that MAS associated with rheumatologic diseases may initially present with normal or elevated platelet counts before progressing to cytopenias.[4] Infection-associated HLH was considered; however, the absence of identifiable infectious triggers and the chronic, indolent course made this less likely, as infection-triggered HLH typically presents acutely with rapid deterioration. This case underscores the diagnostic challenge of MAS, particularly in early or atypical stages, where overlapping features with systemic juvenile idiopathic arthritis, infection, and malignancy can delay diagnosis. Unlike the classical fulminant presentation reported in many studies, our patient demonstrated a gradual evolution of laboratory abnormalities, emphasizing that MAS exists on a clinical spectrum. Early recognition and timely initiation of immunosuppressive therapy are crucial for favorable outcomes, as evidenced by the good response to corticosteroids and methotrexate in our patient, consistent with current literature.

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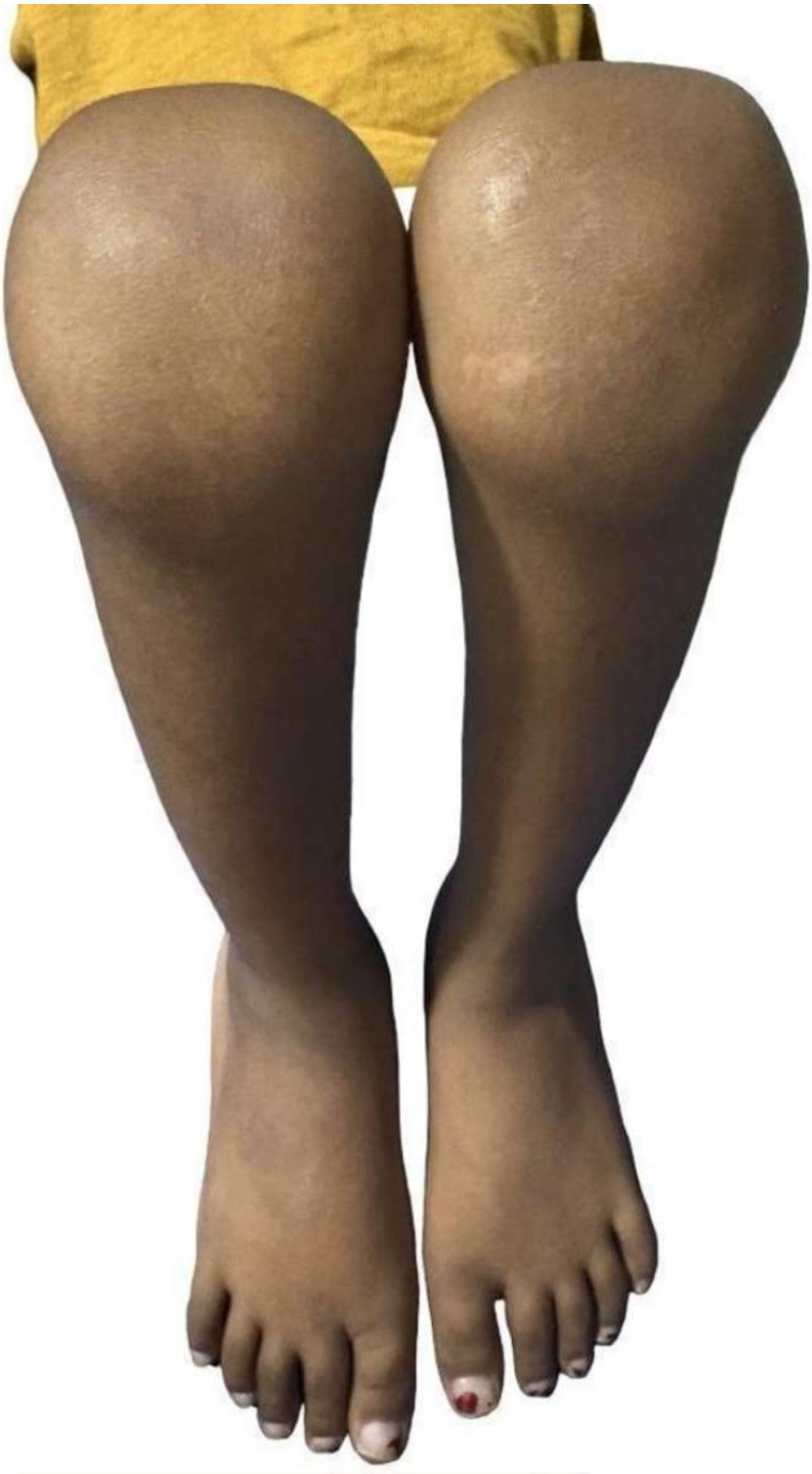

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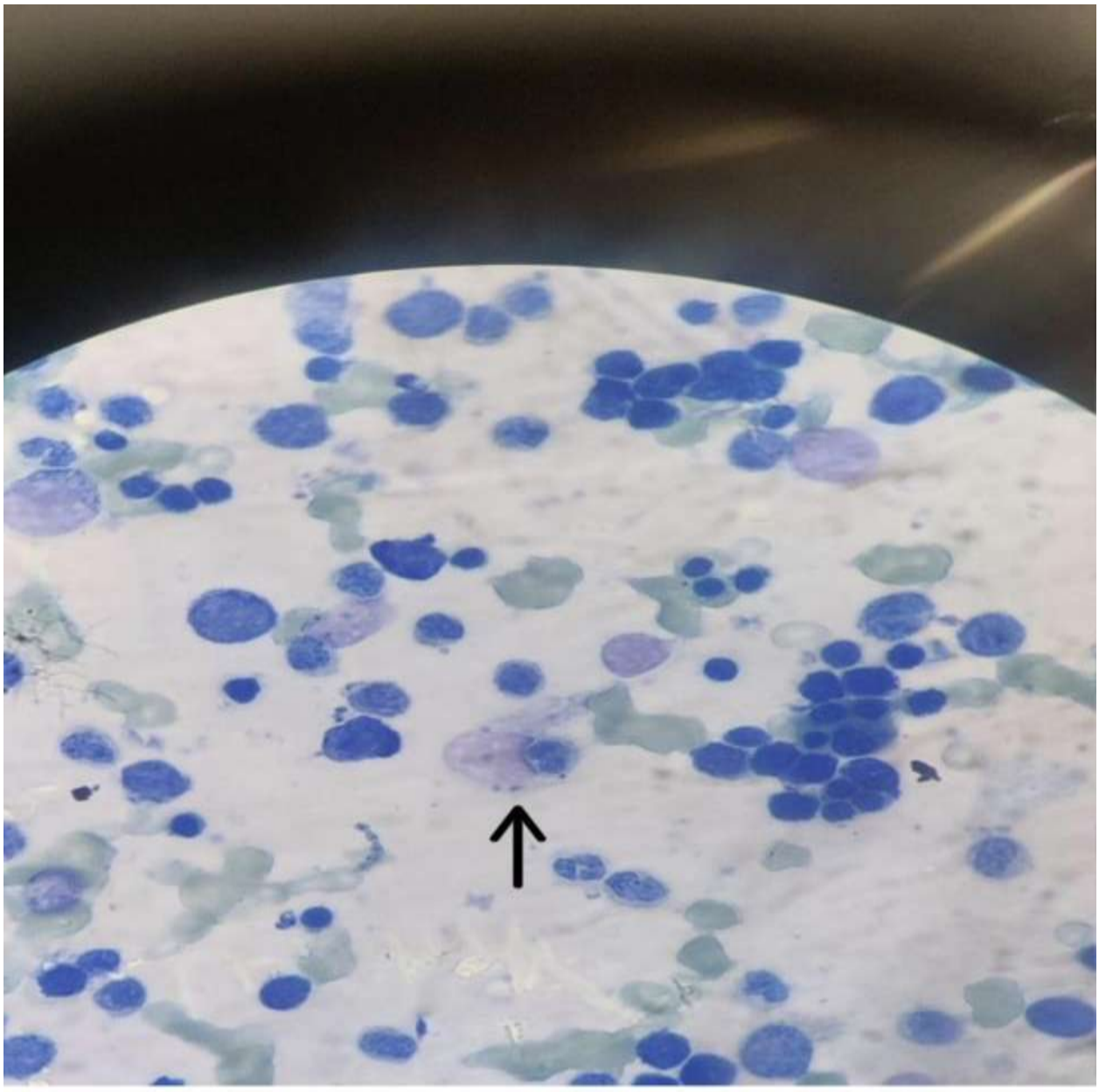

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