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Case Report

Hyperferritinemia Associated with Macrophagic Activation Syndrome (MAS) Complicating Salmonella Gastroenteritis: A Case Report

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Abstract

Macrophage activation syndrome (MAS) is a rare but potentially life-threatening hyperinflammatory condition that can complicate autoimmune diseases, malignancies, and infections. It is considered part of the spectrum of secondary hemophagocytic lymphohistiocytosis (HLH) and may affect both children and adults. Although MAS triggered by bacterial infections is uncommon, prompt recognition is crucial to ensure appropriate management. We report the case of a 7-year-old child admitted to the pediatric emergency department with severe *Salmonella*gastroenteritis complicated by MAS. The patient presented with persistent fever, diarrhea, vomiting, and signs of systemic inflammation. Laboratory investigations revealed pancytopenia, marked hyperferritinemia, and elevated liver enzymes, raising strong suspicion for MAS. Inflammatory markers, including C-reactive protein and procalcitonin, were significantly elevated, and *Salmonella* was isolated through stool culture. Bone marrow examination did not reveal hemophagocytosis; however, its absence did not exclude the diagnosis due to known variability in this finding. Based on the clinical presentation and laboratory findings, a diagnosis of MAS secondary to bacterial infection was established. The patient responded favorably to intravenous antibiotic therapy and supportive care, with rapid clinical and biological improvement. This case highlights the importance of considering MAS in children presenting with sepsis-like symptoms and cytopenias, even when bone marrow findings are inconclusive, particularly in the setting of confirmed bacterial infection.

Keywords: Hemophagocytic Lymphohistiocytosis, Macrophagic Activation Syndrome, Gastroenteritis, Pancytopenia, Hyperferritinemia, Salmonella.

INTRODUCTION

Macrophage activation syndrome (MAS), often considered a form of secondary hemophagocytic lymphohistiocytosis (HLH), is a severe hyperinflammatory reaction that may be idiopathic or triggered by an underlying systemic disease, including autoimmune disorders, infections, or malignancies. It is characterized by the presence of abnormal hemophagocytic macrophages and a state of hypercytokinemia, commonly referred to as a "cytokine storm" [1]. Unlike primary or familial HLH—which typically manifests in early childhood due to genetic mutations affecting the cytotoxic pathway involving perforin—MAS, or secondary HLH, can occur at any age and often arises as a complication of an underlying inflammatory condition [2]. Without early recognition and treatment, MAS can rapidly progress to fatal multiorgan failure.

The clinical and biological features of MAS include persistent fever, marked hyperferritinemia, pancytopenia, disseminated intravascular coagulation (DIC), central nervous system dysfunction, and elevated liver enzymes [3]. Hypertriglyceridemia is also frequently observed, serving as a key diagnostic marker that reflects the metabolic dysregulation associated with the inflammatory response. These clinical signs often overlap with those of the underlying systemic inflammatory disease, making the diagnosis particularly challenging. MAS is increasingly recognized in the context of autoimmune conditions such as systemic lupus erythematosus, Kawasaki disease, and periodic

fever syndromes, as well as in severe infections, including sepsis [4].

In this clinical case, we present the observation of a child admitted with MAS secondary to *Salmonella* gastroenteritis, characterized by extreme hyperferritinemia and significant hypertriglyceridemia. This case highlights the diagnostic value of these biological markers and underscores the urgent need for prompt management to prevent a potentially fatal outcome [5].

PATIENT AND OBSERVATION

This case concerns a 7-year-old patient, fully vaccinated according to the National Immunization Program (NIP), with no significant medical history, who was admitted to the pediatric emergency department for abdominal pain associated with vomiting, acute diarrhea, and a persistent fever lasting five days, unresponsive to symptomatic treatment.

On clinical examination, the patient presented with a temperature of 39.5°C, gingival hypertrophy, and splenomegaly estimated at two finger breadths (TDD). Given the suggestive clinical presentation, a comprehensive laboratory workup was performed. The results revealed pancytopenia, characterized by normochromic, normocytic, aregenerative anemia (hemoglobin: 10.1 g/dL), leukopenia (2,400/µL) with lymphopenia (570/µL), and thrombocytopenia (72,000/µL). Liver function tests indicated hepatic cytolysis, with aspartate aminotransferase (AST) levels elevated to three times the normal value. Acute renal failure was also present. Marked hyperferritinemia (39,450 ng/mL) and hypertriglyceridemia (2 g/L) were observed, alongside an elevated lactate dehydrogenase (LDH) level of 1,816 U/L. Infectious screening revealed negative serologies for HIV and CMV, and negative sputum testing for *Mycobacterium tuberculosis*.

Inflammatory markers were significantly elevated, with procalcitonin at 5.52 ng/mL and C-reactive protein (CRP) at 280 mg/L. A sternal bone marrow aspiration was performed due to the pancytopenia, revealing a normocellular, heterogeneous, and hemodiluted marrow, with a balanced granulocytic lineage, hypoplasia of the erythroblastic lineage, and 2% blast cells. Abdominal ultrasonography demonstrated homogeneous hepatosplenomegaly and a small amount of anechogenic intra-abdominal fluid. Stool culture identified *Salmonella* spp. sensitive to beta-lactam antibiotics.

In light of the association between *Salmonella* gastroenteritis and the severe inflammatory syndrome—marked by hyperferritinemia and hypertriglyceridemia—the diagnosis of macrophage activation syndrome (MAS) was established. Empiric intravenous antibiotic therapy with a third-generation cephalosporin was initiated. The clinical course was favorable, with rapid resolution of fever and gastrointestinal symptoms. Laboratory follow-up showed progressive normalization of parameters, including correction of pancytopenia and renal function, a decrease in LDH from 1,816 U/L to 507 U/L, ferritin reduction from 39,450 ng/mL to 439 ng/mL, and significant improvement in inflammatory markers, particularly CRP (5 mg/L).

Evolution of biological values after treatment:

	Before	**After**
Hemoglobin	10,1 g/dL	12,3 g/dL
Platelets	72000 µL	188 000 µL
Neutrophils	2400 µL	5300 µL
triglycerids	2g/L	1,5g/L
CRP	280 mg/L	6 mg/L
Serum ferritin	39450 ng/mL	439 ng/mL
LDH	1816 U /L	507 U/L

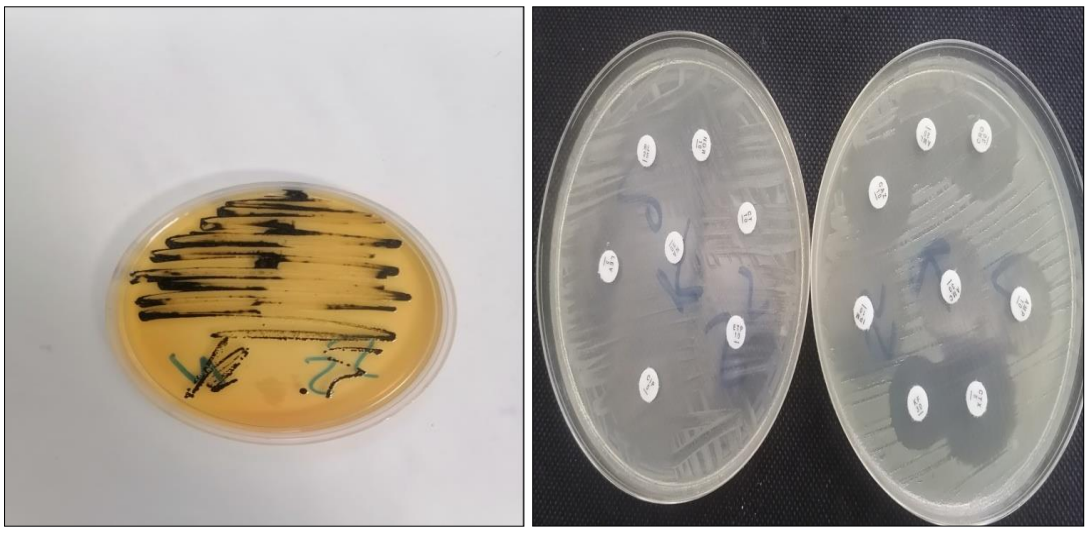

Photo 1: Culture and antibiogram of the Salmonella strain isolated from the patient's stool culture

DISCUSSION

Macrophage activation syndrome (MAS), also referred to as secondary hemophagocytic lymphohistiocytosis (sHLH), is a life-threatening hyperinflammatory condition resulting from excessive immune activation, typically triggered by an underlying systemic disease, infection, or malignancy. Although relatively rare, its actual prevalence is likely underestimated due to diagnostic challenges and overlap with other inflammatory syndromes [6]. MAS is characterized by the uncontrolled proliferation and activation of T lymphocytes and macrophages, leading to a dysregulated immune response and hypersecretion of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, IL-10, IL-12, IL-18, and macrophage colony-stimulating factor [7].

Clinically, MAS presents with persistent high-grade fever, generalized lymphadenopathy, hepatosplenomegaly, and varying degrees of central nervous system involvement, ranging from mild confusion to seizures or coma. In severe forms, hemorrhagic manifestations indicative of disseminated intravascular coagulation (DIC) may occur, along with cutaneous rashes and bleeding from the respiratory and gastrointestinal tracts [8].

Biologically, MAS is marked by pancytopenia; normochromic, normocytic or microcytic aregenerative anemia often accompanied by signs of hemolysis; elevated liver enzymes; and coagulation abnormalities including hypofibrinogenemia and hypertriglyceridemia [3]. Among laboratory findings, hyperferritinemia is considered a hallmark of MAS and serves both as a diagnostic and prognostic marker [5]. In the context of HLH, monocytes and macrophages play a central role by producing and releasing large quantities of ferritin. These elevated ferritin levels are not only reflective of the intense inflammatory state but also contribute to disease progression by further amplifying cytokine expression—a phenomenon known as the "cytokine storm" [9].

Hyperferritinemia is observed in approximately 70% of MAS cases and may reach levels up to tenfold above normal [10], like our patient who had a ferritin value of 39,450 ng/mL. In pediatric HLH patients, ferritin levels serve as a valuable prognostic indicator; a reduction of less than 50% within ten weeks of diagnosis is associated with a 17-fold increased risk of mortality, compared to patients exhibiting a reduction of ≥96% [11]. Moreover, a ferritin level exceeding 10,000 µg/L is regarded as both highly sensitive and specific for diagnosing HLH in children [12]. However, this diagnostic threshold is less reliable in adults, as elevated ferritin levels can also be seen in conditions such as chronic renal failure, certain infections, and hematologic malignancies, with levels sometimes exceeding 50,000 µg/L [13].

Bone marrow examination often reveals the presence of well-differentiated macrophages actively phagocytosing hematopoietic cells—a key diagnostic criterion for MAS [14]. However, the absence of hemophagocytosis in bone marrow samples does not exclude the diagnosis. This finding may be absent due to sampling errors, preferential macrophage infiltration in other tissues (such as the liver, lymph nodes, skin, or lungs), or early-stage disease at the time of evaluation [8], in our case no images of hemophagocytosis were found.

To aid in diagnosis, the International Histiocyte Society has established standardized criteria for HLH [15]. Nevertheless, diagnosing MAS remains complex, particularly in patients with preexisting conditions associated with cytopenias, making differential diagnosis challenging [8]. In cases where hemophagocytosis is not identified initially, further investigations are warranted. If bone marrow findings are inconclusive, biopsy or aspirate from other affected organs should be considered to confirm the diagnosis.

Infectious triggers, particularly viruses such as Epstein-Barr virus (EBV), are commonly implicated in secondary MAS (SAMI). However, MAS has also been documented in bacterial infections involving pathogens typically considered "common," including *Staphylococcus aureus*, *Streptococcus pneumoniae*, and Gram-negative bacilli [16]. In a study conducted in an intensive care unit, bone marrow examination in cytopenic patients with septic shock revealed hemophagocytosis in 60% of cases, underscoring the possibility that MAS is underdiagnosed in sepsis. These findings suggest that in patients with septic syndrome, especially those presenting with high fever, cytopenia, hypertriglyceridemia, and hyperferritinemia, MAS should be considered as a differential diagnosis [17].

SAMI secondary to typhoid fever is rarely reported, and its incidence remains unknown in Morocco. However, a study involving 30 patients in India documented two cases of MAS triggered by *Salmonella* infection [18]. The proposed pathophysiological mechanism includes excessive cytokine production by activated lymphocytes and monocytes, as well as impaired function of natural killer (NK) cells and cytotoxic T lymphocytes [19].

The case of a 7-year-old child with *Salmonella* gastroenteritis presented here in adds to the limited literature on this rare but serious complication. The patient was admitted with persistent high fever, gastrointestinal symptoms, and laboratory features suggestive of MAS, including pancytopenia, elevated liver enzymes, and extreme hyperferritinemia (39,450 µg/L). Hypertriglyceridemia further supported the diagnosis, while the presence of splenomegaly on clinical examination aligned with the typical presentation of MAS. Although bone marrow aspiration

was not performed, the constellation of findings was sufficient to establish a probable diagnosis of MAS secondary to *Salmonella* infection.

Treatment relies on early initiation of appropriate antibiotic therapy based on antimicrobial susceptibility testing, alongside supportive care to manage electrolyte imbalances and organ dysfunctions (e.g., fluid resuscitation, vasopressors, transfusions, ventilatory support). There are no well-defined treatment protocols specific to MAS complicating *Salmonella* infections due to the rarity of the condition. Existing treatment strategies are extrapolated from those used in EBV-associated or non-infectious MAS [20].

Immunomodulatory therapies are typically reserved for severe cases with multiorgan involvement and are initiated only after antibiotic therapy has commenced. These treatments aim to mitigate the cytokine storm and improve survival outcomes. Some reports have documented favorable responses to high-dose corticosteroid therapy alone [21]. More aggressive regimens often involve the addition of cyclosporine A (CsA), which remains the most commonly used adjunct to corticosteroids [22], or etoposide-based protocols such as HLH-94 and HLH-2004, although these carry notable mortality risks [23, 24]. Among biologic therapies, intravenous immunoglobulins (IVIg) have been employed, but their efficacy is contingent upon early administration [25].

In general, outcomes for patients with non-EBV-related SAMI are favorable in 60–70% of cases when appropriate antimicrobial therapy and organ support are provided [26]. The favorable evolution observed in the present case—characterized by rapid defervescence, normalization of blood counts, and resolution of inflammatory markers following intravenous third-generation cephalosporin and supportive therapy—underscores the importance of early recognition and intervention. This case highlights the necessity of considering MAS in children with typhoid fever who present with persistent fever and cytopenia, and it reinforces the value of comprehensive biochemical monitoring, including ferritin and triglyceride levels, in guiding diagnosis and management.

Table 1: Diagnostic Criteria for Macrophage Activation Syndrome: HLH-2004 - Revised Diagnostic Guidelines for HLH

HLH diagnosis can be established if one of the two criteria below is met:
(1) A molecular diagnosis compatible with HLH (i.e., reported mutations found in PRF1 or MUNC13-4), or
(2) The diagnostic criteria for HLH are met (i.e., at least five of the eight criteria listed below are present):
(a) Persistent fever
(b) Splenomegaly
(c) Cytopenia (affecting ≥2 of the 3 cell lines in peripheral blood):
(i) Hemoglobin < 90 g/L (for infants < 4 weeks: <100 g/L)
(ii) Platelets < 100×10^9/L
(iii) Neutrophils < 1.0×10^9/L
(d) Hypertriglyceridemia and/or hypofibrinogenemia:
(i) Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥265 mg/dL)
(ii) Fibrinogen ≤ 1.5 g/L
(e) Hemophagocytosis in the bone marrow* or in the spleen or lymph nodes, with no signs of malignancy
(f) Serum ferritin ≥ 500 μg/L (i.e., 500 ng/mL)
(g) Low or absent NK cell activity (according to local laboratory reference)
(h) Increased serum sIL2Rα level (according to local laboratory reference)

CONCLUSION

Macrophage activation syndrome (MAS) should be considered as a potential complication of typhoid fever, particularly in pediatric patients presenting with a febrile gastrointestinal syndrome accompanied by pancytopenia and hyperferritinemia. Elevated ferritin levels serve not only as a marker of inflammation but also play a direct pathogenic role in the cytokine storm characteristic of hemophagocytic lymphohistiocytosis (HLH). In this context, comprehensive biochemical evaluation is crucial. Hypertriglyceridemia, a hallmark diagnostic criterion for MAS, reflects the extent of macrophage activation and supports the diagnosis. Furthermore, monitoring liver enzymes, lactate dehydrogenase (LDH), and inflammatory markers such as C-reactive protein (CRP) and procalcitonin is essential for assessing disease progression, guiding therapeutic interventions, and evaluating patient prognosis.

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