Pediatric macrophage activation syndrome, recognizing the tip of the Iceberg

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Abstract

Macrophage activation syndrome (MAS) is the name given to secondary hemophagocytic lymphohistiocytosis (sHLH) associated with rheumatic diseases. Previously, MAS has been best studied in children with systemic juvenile idiopathic arthritis (sJIA), who are at high risk of developing MAS. MAS/sHLH is a cytokine storm that results in multi-organ system failure and is frequently fatal. Early diagnosis and treatment is critical for improving survival. Various diagnostic tools have been developed for identifying MAS in the setting of sJIA, as well as for all forms of MAS/sHLH. These are largely based on clinical (e.g., fever) and laboratory features (e.g., cytopenias). None are perfectly sensitive and specific, however, increasing awareness of this condition is also paramount in making the diagnosis. Rare familial forms of HLH can also be diagnosed based on homozygous mutation in genes largely involved in perforin-mediated cytolytic function of lymphocytes (natural killer cells and CD8 T cells). Intriguingly, heterozygous defects in these same genes are frequently identified in patients with sHLH and MAS. Decreased cytolytic function results in prolonged interaction of the lytic lymphocytes and their target antigen presenting cells, thus resulting in the pro-inflammatory cytokine storm believed responsible for the multi-organ failure. Novel cytokine-targeted therapies are currently being explored for a less toxic yet effective alternative to chemotherapeutic approaches to treating children with sHLH/MAS. As increased recognition and diagnosis of MAS is on the rise, an earlier and cytokine-targeted approach to therapy will likely save many lives of children with this disorder.

Keywords: Macrophage activation syndrome, hemophagocytic lymphohistiocytosis, systemic juvenile idiopathic arthritis, cytokine storm, interleukin-1 receptor antagonist

Introduction

Macrophage activation syndrome (MAS), a term often used interchangeably with secondary hemophagocytic lymphohistiocytosis (sHLH), describes a severe hyperinflammatory reaction, which can be idiopathic or triggered by underlying systemic illness (e.g., autoimmune disease, malignancy, infection) that frequently leads to abnormal hemophagocytic macrophages with associated hypercytokinemia, otherwise known as a “cytokine storm.” Unlike primary or familial HLH, which commonly presents during infancy and results from homozygous or compound heterozygous mutations in genes involved in the perforin-mediated pathway of cytolysis shared by both the innate (i.e., natural killer (NK) cells) and adaptive (i.e., cytotoxic CD8 T cells) immune systems (1), MAS can occur at any age and often complicates an underlying systemic inflammatory disorder, most commonly systemic juvenile idiopathic arthritis (sJIA) and its adult equivalent, adult onset Still’s disease (AOSD). If unrecognized and untreated, MAS can lead to multi-organ failure and ultimately death (2-4).

Clinical and laboratory features of MAS include sustained fever, hyperferritinemia, pancytopenia, consumptive coagulopathy mimicking disseminated intravascular coagulation, central nervous system dysfunction, and elevated liver enzymes. Many of these features complicate co-existing systemic inflammatory disease, thus making a diagnosis of MAS difficult (5-9). A majority of clinical data available describes MAS as a complication of sJIA with the prevalence of fulminant MAS in patients with sJIA reported to be about 10%. Subclinical MAS, however, may be present in as many as 30%-40% of children with known or suspected sJIA (2, 8-10). As MAS becomes more clinically recognized, an increasing frequency of occurrence in other systemic inflammatory disorders [i.e., systemic lupus erythematosus (SLE), Kawasaki disease, and periodic fever syndromes] has been reported (Figure 1) (11-14). However, we are likely just beginning to recognize the tip of the iceberg, as many febrile and hyperferritinemic pediatric and adult hospitalized patients with multi-organ failure and systemic inflammation may indeed be suffering from sHLH/MAS, including those with frank sepsis (Figure 2) (15-17).
Diagnostic criteria
Early identification remains diagnostically challenging as there is no single pathognomonic feature of MAS or even a set of universal diagnostic criteria. The clinical similarity of MAS and secondary HLH has led some clinicians to use the longer-standing HLH-2004 diagnostic guidelines, which require 5 of the following 8 criteria to be met for diagnosis: fever, splenomegaly, cytopenias (affecting ≥2 of 3: hemoglobin<90 g/L, platelets<100x10^9/L, neutrophils≤1.0x10^9/L), hypertriglyceridemia (≥2.65 mmol/L) and/or hypofibrinogenemia (≤1.5 g/L), hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK cell activity, and ferritin ≥500 µg/L, and sCD25≥2400 units/mL (Table 1) (18). While specific but insensitive for identifying MAS, strict usage of HLH-2004 criteria may delay diagnosis in patients with a less severe initial presentation (5).

In 2016, an expert consensus panel published a set of validated classification criteria to help distinguish a sJIA flare from MAS. The identification of MAS can be made in a febrile patient with sJIA or suspected sJIA, who has a serum ferritin level >684 ng/mL plus any 2 of the following: platelet count ≤181x10^9/L, aspartate aminotransferase (AST)>48 units/L, triglyceride concentration >156 mg/dL, or fibrinogen ≤360 mg/dL (Table 1) (8, 9). These relatively few total criteria are routinely readily available and timely. While the final MAS criteria for children with sJIA proved to have a sensitivity of 0.73 and specificity of 0.99, emerging clinical practice data suggest that patients with known sJIA treated with anti-IL-1 and anti-IL-6 biologic agents may have alterations in laboratory findings and possibly remain afebrile, which subsequently results in a missed diagnosis of MAS (19). To date, these criteria are yet to be proven to have diagnostic value for other autoimmune diseases and remain limited to children with known or suspected sJIA, with the possible exception of AOSD (3).

The inadequate performance of the MAS classification criteria in daily clinical practice led to a validated, weighted MAS/sJIA (MS) scoring system using the original data set from the 2016 classification criteria. The newer MS scoring system excluded the control sample with systemic infection, which had less pronounced systemic inflammation and subsequently laboratory values, thus creating an inflation effect on the laboratory abnormalities. Central nervous system (CNS) involvement (β-coefficient 2.44), hemorrhagic manifestations (β-coefficient 1.54), active arthritis (β-coefficient −1.30), platelet count (β-coefficient −0.003), lactate dehydrogenase (LDH) (β-coefficient 0.001), fibrinogen (β-coefficient −0.004), and ferritin (β-coefficient 0.0001) are included in the MS score calculation. Each clinical variable is given a binary constant of “1” or “0” based on the presence or absence of the feature and multiplied by the respective β-coefficient. Absolute laboratory values are multiplied by the respective β-coefficient, and all variables are added for a final MS score (Table 1). The sum of the values ranges from −8.4 to 41.8 with a cutoff value of z=−2.1, yielding a sensitivity of 0.85 and specificity of 0.95 in discriminating MAS from an active sJIA flare (20). While the newer MS scoring system potentially may prove applicable to AOSD, it is not intended to be used in other pediatric rheumatic diseases.

MAS complicated by other rheumatic diseases is less commonly reported than sJIA. Comparison of clinical and laboratory data from 38 juvenile SLE patients with definite or probable MAS to controls suggests that with the exception of fever, the other clinical features (i.e., CNS involvement, hemorrhage, hepatomegaly, splenomegaly) have better specificity than sensitivity in distinguishing MAS from an active sJIA flare. Preliminary diagnostic guidelines for MAS as a complication of juvenile SLE requires 1 clinical feature (i.e., fever, CNS involvement, hepatomegaly, splenomegaly, hemorrhage) and 2 laboratory criteria, which includes cytopenia affecting ≥2 cell lines (i.e., hemoglobin ≤90 g/L, platelet≤150x10^9/L, white blood

Figure 1. Macrophage Activation Syndrome (MAS), Hemophagocytic Lymphohistiocytosis (HLH), Cytokine Storm Syndrome publications excluding review articles, as cited in PUBMED and grouped by decade.

Main Points
- Macrophage activation syndrome (MAS) and the related condition of secondary hemophagocytic lymphohistiocytosis (sHLH) are the result of “cytokine storms”, leading to multi-organ system failure and frequently death.

- Novel diagnostic criteria are being developed for the timelier recognition of MAS/sHLH to allow for earlier treatment and improved outcomes.

- Many children with MAS/sHLH possess heterozygous mutations in cytolytic pathway proteins present as homozygous defects in children with familial forms of HLH, thus sharing a similar pathophysiology in many cases.

- Cytokine-targeted approaches (e.g., IL-1, IFNγ) are being explored for safer yet effective therapies for children with MAS/sHLH.

Figure 2. Recognizing the tip of the HLH/MAS iceberg which may include many febrile, hyperferritinemic, hospitalized patients with multi-organ dysfunction syndrome, systemic inflammatory response syndrome, and negative and positive sepsis cultures.
Table 1. Comparison of diagnostic criteria for Macrophage Activation Syndrome (MAS)/Secondary Hemophagocytic Lymphohistiocytosis (sHLH)

| Parameter                              | HLH-2004 | 2016 sJIA/MAS | MAS/sJIA Score | H score |
|----------------------------------------|----------|---------------|----------------|---------|
| Fever °C                               | ≥38.5    | Degree not specified | ---           | 0 (<38.4), 33 (38.4–39.4), of 49 (>39.4) |
| Ferritin                               | ≥ 500 µg/L | > 684 ng/mL | 0.0001* serum level | 0 (<2,000), 2,000–6,000, or 50 (>6,000) |
| Organomegaly                           | Splenomegaly | --- | --- | 0 (no), 23 (hepato- or splenomegaly), 38 (both) |
| Hematologic effects affecting ≥2 of 3# | platelets=181×10^9/L | 0.003* platelet count | 0 (one lineage), 24 (2 lineages), or 34 (3 lineages) |
| Hemorrhagic Manifestations             | ---      | ---           | 1.54*1(yes) or *0(no) | --- |
| Triglyceride Level                     | ≥ 265 mg/dL | > 156 mg/dL | --- | 0 (<1.5 mmol/L), 44 (1.5–4 mmol/L), or 64 (>4 mmol/L) |
| Fibrinogen Level                       | ≤ 1.5 g/L | ≤ 360 mg/dL | 0.004* serum level | 0 (>2.5 g/L) or 30 (≥2.5 g/L) |
| Lactate Dehydrogenase Level            | ---      | 0.001* serum level | --- | --- |
| Aspartate Aminotransferase (AST)       | ---      | > 48 units/L | --- | 0 (<30 IU/L) or 19 (≥30 IU/L) |
| CNS Involvement                        | ---      | ---           | 2.44*1(yes) or *0(no) | --- |
| Active Arthritis                       | ---      | ---           | -1.3*1(yes) or *0(no) | --- |
| Known immunosuppression                | ---      | ---           | 0 (no) or 18 (yes) | --- |
| Histopathology                         | hemophagocytosis | --- | --- | Hemophagocytosis in bone marrow: 0 (no) or 35 (yes) |
| Natural killer (NK) cell activity      | low or absent | --- | --- | --- |
| sCD25                                  | ≥ 2400 units/mL | --- | --- | --- |
| Diagnosis                               | 5 of 8 criteria met | Fever in known or suspected sJIA + Ferritin + 2 of the remaining 4 | Sum of parameters ≥ 169 | Sum of parameters ≥ -2.1 |

#hemoglobin<90 g/L, platelets<100×10^9/L, neutrophils<1.0×10^9/L, %hemoglobin<92 g/L, platelets<110×10^9/L, leukocytes<5.0×10^9/L, MAS, macrophage activation syndrome; HLH, hemophagocytic lymphohistiocytosis; sJIA, systemic juvenile idiopathic arthritis; *multiplication (e.g., 0.0001 times platelet count).
In addition to defects in the perforin-mediated cytolytic pathway, there are other mechanisms by which genetic mutations can trigger MAS and directly affect cells (e.g., macrophages and dendritic cells) of the innate immune system by altering cytokine production via the inflammasome complex (44). Gain of function mutations, as seen in Familial Mediterranean Syndrome (FMF), result in hyperactivation of the NLRC4 inflammasome which can in turn result in MAS. NLRC4 triggers the inflammasome, an innate immune complex that responds via caspase-1 activation and IL-1β and IL-18 secretion (45, 46). Moreover, rare activating mutations in NLR4 itself can lead to an autoimmune disorder complicated by high IL-18 levels and clinical MAS (47). Although the mechanisms have not been worked out as clearly, there are other gene mutations associated with MAS/HLH. These include genes involved metabolism (e.g., SLC7A7), autophagy (e.g., NEMO), and viral control (e.g., CD27) (48). For many patients, the combination of a genetic predisposition, an underlying inflammatory state, and a triggering agent (e.g., infection) likely contribute to the cytokine storm seen in MAS (41).

**Pathophysiology / Immunology**

The acute phase of MAS is often associated with markedly elevated levels of pro-inflammatory cytokines like interferon-gamma (IFNγ), which are thought to be the primary drivers of pro-inflammatory (M1) macrophages (33, 49). The working hypothesis suggests that macrophages produce an array of cytokines, notably tumor necrosis factor (TNF) and various interleukins (i.e., IL-6, IL-1, and IL-18), which trigger a cascade of inflammatory pathways and ultimately create a cytokine storm (49). The pro-inflammatory cytokine environment, particularly IL-6, has been shown to decrease the cytokolytic function of the NK cell (50). The inability of NK cells and cytolytic CD8 T cells to lyse infected and otherwise APCs results in an increased prevalence of heterozygous mutations in known fHLH genes found in MAS patients. Defects in the perforin-mediated cytolytic pathway result in an inability of cytolytic lymphocytes to lyse the infected antigen presenting cell (APC), which subsequently results in a prolonged cell-to-cell interaction causing a pro-inflammatory cytokine storm that ultimately leads to the clinical sequelae seen in MAS (34, 35). Heterozygous mutations in fHLH genes (e.g., PRF1, LYST, RAAB27A, UNC13D, STXBP2, STX11) may be found in as high as 40% of patients with MAS (36, 37). This is likely significantly higher than the reported combined rates of these mutations (~15%) in the general population or disease control groups (38). As in adult onset HLH, heterozygous mutations in fHLH genes may also contribute to lymphoma development (39, 40). As in fHLH, these heterozygous hypomorphic and dominant-negative gene mutations can alter cytokolytic function in NK cells and CD8 T cells (38). Using a threshold model of disease (41), a combination of a chronic inflammatory state, such as in sJIA or SLE, with a genetic predisposition, and/or a triggering infection may result in fatal MAS or sHLH as evidenced in the increased percentages of PRF1 and UNC13D heterozygous mutations in cohorts of sJIA patients who develop MAS (42, 43).

With this in mind, a significant rise in serum ferritin (e.g., >10,000 ng/mL) in the setting of a hospitalized febrile patient is an inexpensive, rapid screening tool for MAS (28). With a cut-off value of ≥ 627 ng/mL for screening with a set sensitivity (0.95), the ferritin level alone had a specificity of 0.89 in identifying cases of all-cause MAS as compared to febrile hospitalized children (29). In combination with the erythrocyte sedimentation rate (ESR), the ferritin to ESR ratio has been shown to be both sensitive and specific in distinguishing MAS in sJIA from an active sJIA flare (29, 30). The ESR may initially be elevated but can drop rather quickly and be surprisingly low with MAS. Consumptive coagulopathy, a hallmark feature of MAS, leads to fibrinogen degradation and results in a drop in ESR (31-33). Unlike in other systemic inflammatory diseases, a combination of a high serum ferritin and low ESR may help confirm a diagnosis of MAS.

**Histopathologic criteria**

Evidence of macrophage hemophagocytosis in the bone marrow aspirate

**Clinical Criteria**
- Fever (>38°C)
- Hepatomegaly (≥ 3 cm below the costal arch)
- Splenomegaly (≥ 3 cm below the costal arch)
- Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
- Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)

**Laboratory Criteria**
- 2 of 3: white blood cell count ≤ 4.0 × 10⁹/L, hemoglobin ≤ 90 g/L, or platelet ≤ 150 × 10⁹/L
- Aspartate aminotransferase (AST) (>40 units/L)
- Lactate dehydrogenase (LDH) (>567 units/L)
- Fibrinogen ≤ 1.5 g/L
- Triglycerides > 178 mg/dL
- Ferritin > 500 μg/L

**Diagnosis of MAS if 1 Clinical + 2 Laboratory OR**

**Genetics**

The clinical and etiologic overlap between MAS and fHLH is significant, and includes an increased prevalence of heterozygous mutations in known fHLH genes found in MAS patients. The working hypothesis suggests that macrophages produce an array of cytokines, notably tumor necrosis factor (TNF) and various interleukins (i.e., IL-6, IL-1, and IL-18), which trigger a cascade of inflammatory pathways and ultimately create a cytokine storm (49). The pro-inflammatory cytokine environment, particularly IL-6, has been shown to decrease the cytokolytic function of the NK cell (50). The inability of NK cells and cytolytic CD8 T cells to lyse infected and otherwise APCs results in a prolonged cell-to-cell interaction causing a pro-inflammatory cytokine storm that ultimately leads to the clinical sequelae seen in MAS (34, 35). Heterozygous mutations in fHLH genes (e.g., PRF1, LYST, RAAB27A, UNC13D, STXBP2, STX11) may be found in as high as 40% of patients with MAS (36, 37). This is likely significantly higher than the reported combined rates of these mutations (~15%) in the general population or disease control groups (38). As in adult onset HLH, heterozygous mutations in fHLH genes may also contribute to lymphoma development (39, 40). As in fHLH, these heterozygous hypomorphic and dominant-negative gene mutations can alter cytokolytic function in NK cells and CD8 T cells (38). Using a threshold model of disease (41), a combination of a chronic inflammatory state, such as in sJIA or SLE, with a genetic predisposition, and/or a triggering infection may result in fatal MAS or sHLH as evidenced in the increased percentages of PRF1 and UNC13D heterozygous mutations in cohorts of sJIA patients who develop MAS (42, 43).

**Table 2. Proposed diagnostic criteria for Macrophage Activation Syndrome complicating Systemic Lupus Erythematosus**

| Clinical Criteria | Fever (>38°C) |
|-------------------|---------------|
|                   | Hepatomegaly (≥ 3 cm below the costal arch) |
|                   | Splenomegaly (≥ 3 cm below the costal arch) |
|                   | Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding) |
|                   | Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma) |

| Laboratory Criteria | 2 of 3: white blood cell count ≤ 4.0 × 10⁹/L, hemoglobin ≤ 90 g/L, or platelet ≤ 150 × 10⁹/L |
|---------------------|-----------------------------------------------|
|                     | Aspartate aminotransferase (AST) (>40 units/L) |
|                     | Lactate dehydrogenase (LDH) (>567 units/L) |
|                     | Fibrinogen ≤ 1.5 g/L |
|                     | Triglycerides > 178 mg/dL |
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known to successfully modify disease activity in a milieu of rheumatic diseases (e.g., RA, JIA, uveitis) (54, 55). Like TNF, IL-6 producing macrophages have been found in the liver of MAS patients (53). Increased levels of IL-6 have also been reported in the serum of sJIA and in sepsis patients (56-58). Despite the association of IL-6 levels and MAS, the role of IL-6 in the pathogenesis of disease is not well-understood. It remains unknown whether macrophages are the main cellular sources of IL-6 in MAS patients.

As members of the IL-1 family of cytokines, IL-1β and IL-18 are potent inducers of IL-6 production in monocytes and macrophages (59, 60). Levels of IL-1β and IL-18 are frequently markedly increased in patients with active sJIA and MAS (61-66). Shimizu et al. (64) used the ratio of IL-18 to IL-6 to predict the development of MAS, noting higher IL-18 levels during the active phase of MAS. Patients within this cohort, who had higher levels of IL-18, were more likely to develop MAS following treatment with IL-6 blockade (i.e., tocilizumab), suggesting that IL-18, rather than IL-6, may play a dominant role in the pathogenesis of MAS. Likewise, while IL-18 is elevated in children with sJIA, the serum levels are significantly higher in sJIA that is complicated by active MAS (66). It is important to understand the mechanism behind the uncontrolled cytokine storm seen in MAS to target specific cytokines upstream and prevent further stimulation of the activated pro-inflammatory M1 macrophages (33).

Treatment

Historically, the treatment of MAS has been focused on controlling the underlying trigger, such as infection or sJIA treatment. However, not all cases present with a known pathogen or with a known etiology, making the treatment of the underlying trigger virtually impossible. Many rheumatologists have shifted toward cytokine-specific therapies in conjunction with treatment of the underlying triggering disease, if it is known. This differs from the HLH-2004 treatment protocol often recommended by oncologists, in which patients receive initial treatment with etoposide and dexamethasone (previously cyclosporine as well) for 8 weeks treatment with etoposide and dexamethasone if it is known. This differs from the HLH-2004 treatment of the underlying triggering disease, cytokine-specific therapies in conjunction with treatment of the underlying trigger virtually impossible. Many rheumatologists have shifted toward cytokine-specific therapies in conjunction with treatment of the underlying triggering disease, if it is known. This differs from the HLH-2004 treatment protocol often recommended by oncologists, in which patients receive initial treatment with etoposide and dexamethasone (previously cyclosporine as well) for 8 weeks treatment with etoposide and dexamethasone if it is known. This differs from the HLH-2004 treatment of the underlying triggering disease, cytokine-specific therapies in conjunction with treatment of the underlying trigger.
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