

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 cytotoxicity 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).

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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 $< 100 \times 10^9/L$, neutrophils $< 1.0 \times 10^9/L$), hypertriglyceridemia (≥ 265 mg/dL) 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 $\mu\text{g/L}$, 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 $\leq 181 \times 10^9/L$, 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 ≥ -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 SLE 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, platelets $\leq 150 \times 10^9/L$, white blood

MAS/HLH/CSS Articles by Decade

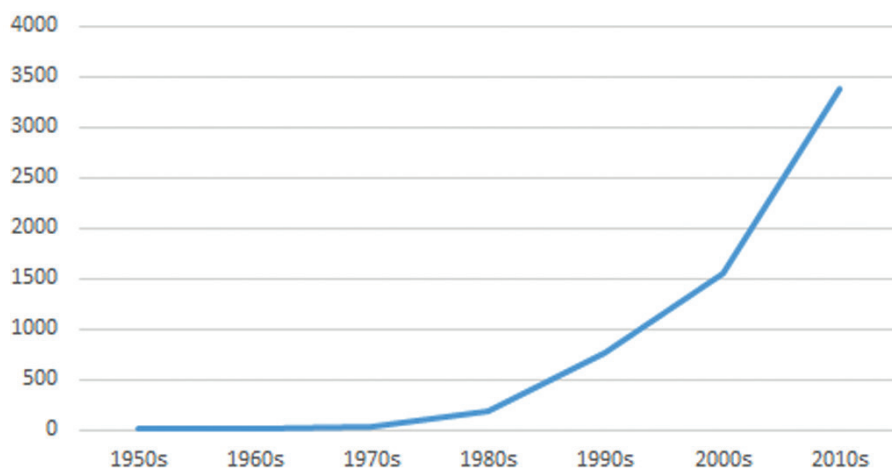


Figure 1. Macrophage Activation Syndrome (MAS), Hemophagocytic Lymphohistiocytosis (HLH), Cytokine Storm Syndrome publications excluding review articles, as cited in PUBMED and grouped by decade.

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, IFN γ) are being explored for safer yet effective therapies for children with MAS/sHLH.

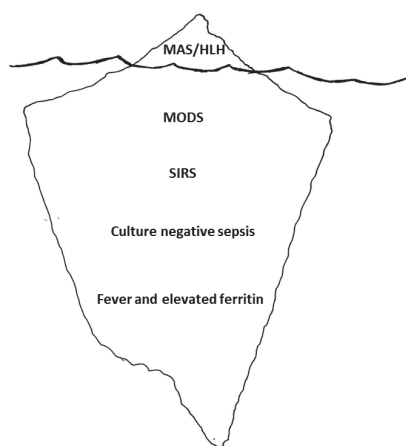


Figure 2. Recognizing the tip of the HLH/MAS iceberg which may include many febrile, hyperferritinemic, hospitalized patients with multi-organ dysfunction syndrome, systemic inflammatory response syndrome, and negative and positive sepsis cultures.

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)
Hematology	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 in bone marrow or spleen or lymph nodes	---	---	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 ≥ - 2.1	Sum of parameters ≥ 169

#hemoglobin<90 g/L, platelets<100×10⁹/L, neutrophils <1.0×10⁹/L; %hemoglobin<92 g/L, platelets<110×10⁹/L, leukocytes <5.0×10⁹/L; MAS, macrophage activation syndrome; HLH, hemophagocytic lymphohistiocytosis; sJIA, systemic juvenile idiopathic arthritis; *multiplication (e.g., 0.0001 times platelet count).

cells (WBC)≤4.0×10⁹/L), hypertriglyceridemia (≥178 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L), AST>40 units/L, increased LDH>567 units/L, hyperferritinemia ≥500 µg/L, or evidence of macrophage hemophagocytosis in the bone marrow aspirate (Table 2) (14). These proposed guidelines are based on a small sample size with a limited control group and have not been validated. The clinical utility of the Parodi et al. (14) diagnostic criteria for MAS in juvenile SLE remains unclear.

Hemophagocytosis, defined as the engulfment of blood cells [e.g., red blood cells (RBC), WBC, platelets] by macrophages has been widely associated with the development of MAS in patients with sJIA and other rheumatologic diseases (8, 9, 14, 21, 22). Histopathology may reveal characteristic increased hemophagocytic activity in the bone marrow, liver, and spleen

with positive CD163 (histiocyte) staining, although hemophagocytosis may not be present in the initial stages and is neither sensitive nor specific for MAS (1, 23, 24). Detection of activated lymphocytes and hemophagocytosis by other means, including serum laboratory tests, includes soluble interleukin 2 receptor alpha chain (sCD25) and soluble CD163 (sCD163), a high affinity scavenger receptor for hemoglobin-haptoglobin complexes. Both of these parameters may be elevated, which suggests that sCD25 and sCD163 may be more sensitive in the detection of MAS. These tests are only performed at select sites, making them costly with a long turnaround time for results, thus leading to a delay in diagnosis and ultimately treatment (25, 26).

In the absence of a gold-standard diagnostic test and overlap of underlying disease man-

ifestations and MAS, the HScore utilizes a scoring system comprised of 9 variables [i.e., 3 clinical (fever, known underlying immunosuppression, and organomegaly), 5 biologic (triglyceride level, ferritin, AST, fibrinogen, and cytopenia), and 1 histopathologic (i.e., hemophagocytosis on bone marrow aspirate)] (Table 1). Each variable is further stratified based on the level range, assigning a numerical value ranging from 0 to 64 to each variable for a maximum of 250. Fardet et al. (27) found that a score of 169 corresponded to a sensitivity of 93% and specificity of 86%, proving to be 90% accurate in correctly diagnosing sHLH. These criteria were developed in adults, many with oncologic conditions, and their ease and utility in pediatric sHLH/MAS is unknown. A simpler and timely set of criteria of sHLH in a broad array of disorders is needed.

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)
Laboratory Criteria	Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)
	2 of 3: white blood cell count ≤4.0×10 ⁹ /L, hemoglobin ≤90 g/L, or platelet ≤150×10 ⁹ /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

Histopathologic criteria Evidence of macrophage hemophagocytosis in the bone marrow aspirate

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. Gorelik et al. (30) reported 100% sensitivity and specificity with a ratio of 80 in a small cohort of sJIA patients. Recently, Eloiseily et al. (29) found, using 2 larger cohorts, a ferritin to ESR ratio of 21.5 (ng/mL divided by mm/hr) was 82% sensitive and 78% specific for diagnosing MAS in sJIA compared to active sJIA without MAS. The ferritin to ESR ratio shows promise as a generalizable, inexpensive, and rapid screening calculation that may lead to an earlier diagnosis and ultimately more timely initiation of treatment in MAS, thereby improving overall patient outcomes.

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. 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*, *RAB27A*, *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 cytolytic 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).

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 *NLRC4* itself can lead to an autoinflammatory 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 cytolytic function of the NK cell (50). The inability of NK cells and cytolytic CD8 T cells to lyse infected and otherwise APCs results in prolonged cell-to-cell interactions and amplification of a pro-inflammatory cytokine cascade, which ultimately leads to the activation of macrophages, causing hemophagocytosis and multi-organ dysfunction. In contrast to the pro-inflammatory macrophages, some macrophages exhibit anti-inflammatory phenotype (M2) with upregulated CD163 receptors and likely serve to dampen the immune response through hemophagocytosis (51, 52).

Expression of TNF by hemophagocytic macrophages was reported in the liver of MAS patients (53). Elevated levels of TNF have been found in patients with other rheumatic diseases [e.g., rheumatoid arthritis (RA)] and are

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-1 β and IL-18 are potent inducers of IL-6 production in monocytes and macrophages (59, 60). Levels of IL-1 β 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 and possibly intrathecal methotrexate and prednisolone if CNS involvement is suspected. Patients who do not achieve remission are then bridged to receive bone marrow transplants (18). Mortality rates in patients treated using the HLH 2004 protocol remain high, with a 5-year survival rate of 64% in children with sHLH (67).

In addition to broadly immunosuppressive medications, such as corticosteroids and cy-

closporine, cytokine-specific therapy (e.g., anakinra) may prove to be more effective in dampening the overly active immune system. Anakinra is a recombinant IL-1 receptor antagonist targeting both IL-1 α and IL-1 β cytokines used off-label in patients with sJIA and less commonly in patients with MAS, either in association with sJIA or other etiologies (68-70). Efficacy data in the treatment of MAS with anakinra is limited to retrospective data, but many patients achieve disease remission with normalization of lab abnormalities and fever despite the poor prior response to more traditional therapies (69, 71). Earlier initiation of anakinra within 5 days of hospitalization was associated a statistically significant reduction in mortality among patients with non-malignancy associated MAS (72).

Likewise, canakinumab is a monoclonal antibody that specifically targets only the IL-1 β cytokine and is a common treatment target in patients with sJIA. Patients with sJIA treated with either anakinra or canakinumab remain at risk for MAS, suggesting that IL-1 receptor is not the sole contributor to the pathogenesis of MAS and that the increased risk may be dose dependent (19, 68). Treatment with recombinant IL-18 binding protein (IL-18bp) in combination with anakinra successfully improved life-threatening hyperinflammation in a patient with sJIA and refractory MAS, suggesting that IL-18 may also stimulate the inflammatory cascade leading to MAS in patients with sJIA (46). Similarly, IL-18bp has been known to effectively treat a child with an autoinflammatory disorder and refractory MAS (73).

Tocilizumab is a monoclonal antibody that targets the IL-6 receptor and is approved for use in RA, giant cell arteritis, polyarticular JIA, and sJIA (74). Despite its success in treating acute sJIA, patients with sJIA who are treated with tocilizumab remain at risk for MAS, which suggests that IL-6 blockade alone is insufficient to control the inflammatory cascade (75-77). These patients tend to be afebrile and had lower cell counts and ferritin levels with higher liver enzymes (19, 76). The mechanism of IL-6 in the pathogenesis of MAS remains controversial. Maude et al. (78) reported rapid resolution of HLH-like cytokine release syndrome (CRS) following the administration of tocilizumab in one patient with drug-induced (i.e., blinatumomab) cytokine storm. IL-6 blockade has similarly shown efficacy in CAR T cell therapy-triggered CRS (78). The utility of IL-6 blockade in other forms of sHLH/MAS remains unknown at present, but targeting other cytokines for treating sHLH/MAS are currently being explored.

While successful treatment of MAS with etanercept, a TNF receptor antagonist, has been reported (79), other studies have shown that it may trigger or worsen disease progression (80). Thus, the role of TNF and its blockade in MAS remains unclear. By comparison, targeting IFN γ with the monoclonal antibody emapalumab (81) has recently been approved by the FDA for treating fHLH; its role in sHLH/MAS is under exploration. Similarly, inhibition of cytokine signaling via JAK-STAT inhibitors may also have a future role in treating sHLH/MAS (82). Thus, the future of cytokine-targeted therapies looks bright for treating patients with frequently fatal disorders, such as sHLH and MAS.

Anecdotally, cytokine-specific therapies in combination with treatments for the underlying disease appear to be effective in reducing mortality rates and improving overall morbidity outcomes in children with MAS. Further studies and clinical trials are needed to better assess the role of various pro-inflammatory cytokines in the pathogenesis of MAS and to determine their clinical relevance. Ultimately, a personalized medicine approach with a variety of cytokine targeting therapeutics may be available for various forms of sHLH/MAS.

Conclusion

MAS is a potentially fatal inflammatory condition that can lead to multi-organ failure if it is treated inadequately. In the absence of generalizable validated diagnostic criteria, its recognition is often delayed. Clinical overlap with fHLH suggests that MAS is on one end of the same disease spectrum. Recognition of the pathogenesis of MAS can guide diagnosis and direct therapy toward target specific treatment. A common hypothesis to understand the pathophysiology of MAS proposes a defect in lymphocyte cytolytic activity. Normally, cytolytic cells induce cell apoptosis in infected or activated APCs. In an infected or inflammatory state, cytolytic cells may induce apoptosis in activated macrophages and dendritic cells and serve to control the inflammatory response. A defect in the cytolytic function may result in overstimulation of the immune system leading to the multi-organ failure seen in MAS. The cytokine storm (i.e., IL-1, IL-6, IL-18) results in activation of macrophages, causing hemophagocytosis, and contributes to multi-organ dysfunction. Specific heterozygous gene mutations in fHLH-associated cytolytic pathway genes (e.g., *PRF1*, *UNC13D*) have been linked to a substantial subset of MAS patients. These mutations cause defects in various proteins responsible for the production and transport of granules leading to the apoptosis of target cells. In addi-

tion, mutations activating the inflammasome complex lead to high IL-18 levels responsible for MAS pathophysiology. Early recognition and prompt treatment with cytokine-specific therapy (e.g., anakinra, IL-18bp) in MAS is critical in maximizing outcomes with this potentially life-threatening disease. Future studies are needed to compare existing diagnostic criteria to develop a set of uniform criteria that may be applied across all rheumatic diseases and other forms of sHLH/MAS. Ultimately, tailored therapy for individual sHLH/MAS patients based on genetics, underlying disorders, and triggers (e.g., infections) will likely optimize outcomes (83).

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