Review

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Macrophage Activation Syndrome in Autoimmune Disease

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Abstract
Macrophage activation syndrome (MAS) is a phenomenon characterized by cytopenia, organ dysfunction, and coagulopathy associated with an inappropriate activation of macrophages. Current diagnostic criteria are imprecise, but the syndrome is now recognized as a form of hemophagocytic lymphohistiocytosis that is characteristically associated with autoimmune diatheses. The diagnosis of incipient MAS in patients with autoimmune disease requires a high index of suspicion, as several characteristics of the disorder may be present in the underlying condition or infectious complications associated with the treatment thereof. Proposed treatment regimens include aggressive approaches that require validation in future controlled studies. This review discusses the major aspects of the pathophysiology, diagnosis, and management of MAS with a focus on the association with autoimmune disease.

Introduction

The central role of macrophage activation in a hemophagocytic syndrome associated with pediatric rheumatic diseases was reported in 1985 [1], although the first descriptions of the disorder may have been as early as the mid-1970s [2, 3]. Subsequent work on the clinical entity now known as macrophage activation syndrome (MAS) has demonstrated that it may be appropriate to classify MAS as a secondary form of hemophagocytic lymphohistiocytosis (HLH). In this review, we will discuss aspects of the pathophysiology, diagnosis, and contemporary management of MAS/secondary HLH with a focus on associations with rheumatologic disease, and will accordingly examine the published literature using the MAS terminology with forays as appropriate into the literature accompanying HLH.

Case Definition and Epidemiology

MAS is a phenomenon characterized by cytopenia, organ dysfunction, and coagulopathy associated with inappropriate activation of macrophages. The current clas-

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Table 1. 2004 Criteria for the diagnosis of HLH [5, 60]

Molecular diagnosis consistent with HLH *or* five of the eight following criteria
Fever
Splenomegaly
Peripheral cytopenia in 2 or more lineages
Hb <10.0 g/dl (or 9.0 g/dl in infants <4 weeks)
Platelets <100 × 10^6/μl
Neutrophils <1.0 × 10^6/μl
Hypertriglyceridemia *or* hypofibrinogenemia
Triglycerides ≥265 mg/dl
Fibrinogen ≤150 mg/dl
Hemophagocytosis
Bone marrow
Spleen
Lymph node
CSF
Low or absent NK-cell activity
Ferritin ≥500 μg/dl
Soluble CD25 ≥2,400 U/ml

Table 2. Proposed criteria for the diagnosis of MAS complicating sJIA (at least two criteria must be fulfilled)

Laboratory criteria	Value
Relative decrease in platelet count	≤262 × 10^6/μl
Elevations in aspartate aminotransferase	>59 U/l
Decreased leukocyte count	≤4.0 × 10^6/μl
Hypofibrinogenemia	≤250 mg/dl

Clinical criteria	Manifestation
Central nervous system dysfunction	irritability headache lethargy disorientation seizures coma
Hemorrhages	ecchymoses purpura mucosal bleeding
Hepatomegaly	≥3 cm below the costal margin

sification of MAS is imprecise, however, it is included among the reactive hemophagocytic syndromes, and the case definition generally proceeds according to the revised diagnostic criteria for HLH (table 1) [4, 5]. The term 'macrophage activation syndrome' was used in a description of the disorder by Albert et al. [6] in 1992 and furthered by Stephan et al. [7, 8] in their 1993 description of 4 pediatric patients suffering from the disorder as a complication of autoimmune disease characterized by a proinflammatory milieu [9, 10]. This terminology remains prevalent in the rheumatology literature, whereas syndromes described in the hematology and infectious disease literature often describe a similar phenomenon as secondary HLH [11]. It is now recognized that MAS is a form of secondary HLH. Some authors suggest that the terms are interchangeable [12–15], whereas others describe MAS as a distinct subset of secondary HLH [16, 17], and still others highlight the heterogeneity of disorders described by both terms and call for revised terminology based more precisely on pathophysiology [18–20].

Accordingly, the current diagnostic scheme remains a work in progress, and several groups have emphasized challenges in applying the most recent classification criteria for HLH to MAS. For example, systemic juvenile idiopathic arthritis (sJIA) is among the most frequent rheumatologic associations with MAS [20, 21]. However, sJIA is independently associated with anemia and hyperferritinemia [22] in the absence of MAS, and frequently is associated with leukocytosis [23]. Each of these features is relevant to the HLH-2004 diagnostic criteria, and the overlap in clinical features can contribute to difficulty in recognizing the onset of MAS [24]. Similarly, coagulopathies are common in MAS and other disorders in the differential diagnosis for HLH, thereby complicating attempts at obtaining tissue samples for histological diagnosis that may even then be prone to sampling error and a lack of specificity [25, 26].

To address these concerns and further refine the definition and classification of the disorder in the subset of patients with sJIA-associated MAS, Ravelli et al. [27] examined historical data from 74 patients with presumed MAS and 37 control patients with sJIA and high disease activity. Using a 'classification criteria approach', the authors proposed a set of four laboratory criteria and three clinical criteria for the diagnosis of MAS complicating sJIA (table 2). In their systemic evaluation, Ravelli et al. [27] also identified a number of characteristic findings on routinely available studies that, while not included in the formal proposed criteria, are associated with the syndrome and may contribute to the index of suspicion (table 3).

These criteria await prospective validation, and the degree to which they might be predictive in MAS associated with rheumatologic disorders other than MAS is unclear. For example, the same group later reported on historical data from pediatric patients suffering from MAS

associated with systemic lupus erythematosus (SLE). They found that while MAS associated with SLE shared many clinical characteristics with sJIA-associated MAS, the differences were sufficient to render the proposed sJIA-associated MAS criteria inapplicable to SLE-associated MAS [20].

The epidemiology of MAS in autoimmune diseases [28–30] remains an open question in many cases. To date, the syndrome has been best studied in sJIAs, with estimates of clinically apparent MAS ranging from 7 to 13% [24, 31]. Furthermore, subclinical marrow evidence of MAS was present in >50% of patients with sJIA in one series [24]. However, MAS has been reported in a wide spectrum of rheumatologic disorders, from the primarily pediatric disorder of Kawasaki disease to the seronegative spondyloarthropathies in adults (table 4).

Comprehensive published data on MAS in other autoimmune disorders [32] are often lacking, and the calculation of quantitative estimates of the incidence and prevalence of MAS is further complicated by an evolving nomenclature and the heretofore prominent absence of clearly defined diagnostic criteria [14, 20, 23]. In the case of sJIA and Still's disease, it has been proposed that MAS is not a distinct disorder but comprises one end of a spectrum of disease activity [24, 33].

Table 3. Laboratory features not included among diagnostic criteria characterizing MAS complicating sJIA [27]

	Sensitivity	Specificity
ESR ≤50 mm/h	0.79	0.8
Alanine aminotransferase ≥40 U/l	0.81	0.91
Bilirubin ≥1.2 mg/dl	0.75	1
Lactate dehydrogenase ≥900 U/l	0.75	0.93
Albumin ≤2.5 g/l	0.35	0.95
Serum sodium ≤130 mEq/l	0.67	1

Table 4. Autoimmune diseases for which an association with MAS has been reported

Autoimmune diseases	References
Dermatomyositis	85
Kawasaki disease	44, 86, 87
SLE	20, 44, 57, 86, 88–92
Adult-onset Still's disease	93
Ankylosing spondylitis	94
Sarcoidosis	95
Inflammatory bowel disease	96, 97
Enthesitis-related arthritis	31
Undefined autoimmune disease	57
Polyarticular JIA	98
sJIA/Still's disease	8, 14, 15, 31, 33, 40, 44, 50, 53, 57, 75, 93, 99–109

Pathophysiology

Microscopic descriptions of erythrophagocytosis by reticular macrophages in hemophagocytic syndromes were reported at least as early as 1939 [34]. Despite 70 years of study, however, the pathophysiology of MAS and other hemophagocytic syndromes remains poorly understood, and much of the understanding of MAS derives from the HLH literature [14].

Overview of Macrophage Activation

Not surprisingly, high levels of several T-cell-driven macrophage-stimulatory chemokines and cytokines may be found in hemophagocytic syndromes, including IFN-γ, MCP-1, and M-CSF [35–38]. The central role of T cells in the hemophagocytic disorders is further illustrated by the diagnostic and prognostic significance of elevated serum levels of the IL-2 receptor, CD25 [39]. Conversely, elevated levels of several macrophage-driven proinflammatory cytokines are present in many cases, including IL-6, IL-12, IL-18, and TNF-α [37, 40, 41], and the presence of TNF-α and IL-6 expression by CD68+ macrophages has been demonstrated in the hepatic parenchyma of patients with hemophagocytic syndromes [42]. The role of IL-1 is less clear in hemophagocytic syndromes, being elevated in some cases and normal in others, perhaps reflecting heterogeneity in the disorders [37, 43]. Striking proliferation of CD163+ hemophagocytic macrophages in marrow and lymphoid tissues is a central feature of hemophagocytic disorders [44, 45]. The literature suggests that these cells may not be the antigen-presenting cells (APCs) responsible for initiating the syndrome [15].

Intriguingly, CD163 is associated with the 'alternate' pathway of macrophage differentiation, traditionally leading to an anti-inflammatory phenotype [46]. Perhaps counterintuitively, a subgroup of patients with sJIA patients at higher presumed risk for MAS were found to express higher levels of genes associated with negative feedback regulation of inflammation [47]. The authors specu-

Table 5. Established genetic causes for familial HLH

Genetic causes	References
Monogenic defects in familial HLH	
Perforin mutations	49
Syntaxin-11	110
MUNC13-4 abnormalities	52, 53, 110, 111
Monogenic periodic fever syndromes	
CINCA/NOMID syndrome	31
Hyper-IgD syndrome	38
Monogenic primary immunodeficiencies	
Griscelli syndrome	112
X-linked lymphoproliferative disease	60, 68
Immunodeficiency, centromeric region instability, and facial anomalies	113
Adenosine deaminase deficiency	114
Chediak-Higashi syndrome	115
Hermansky-Pudlak syndrome (type II)	116

least three genes have been identified as causative in familial HLH, while several monogenic disorders and primary immunodeficiencies associated with defective cytotoxic function may present with hemophagocytic syndromes as a primary manifestation of the underlying molecular defect (table 5).

Extension of these data to MAS confirmed that diminished NK-cell activity was strongly associated with the development of MAS in sJIA [18, 19]. Even in the absence of clinical MAS, defects in both CD8+ cytotoxic function and NK-cell function can distinguish sJIA from other rheumatologic syndromes in the JIA classification scheme of the International League of Associations for Rheumatology that are far less commonly associated with MAS [50, 51]. Interestingly, it has now been recognized that polymorphisms in some of the genes associated with familial hemophagocytosis syndromes may also be associated with the development of MAS in sJIA [52, 53].

late that inflammation initiated by Toll-like receptor activation events and characterized by expression of IL-1 and IL-6 may lead to negative feedback responses that direct macrophages to a CD163+ 'scavenger' phenotype, priming the progression to the clinically apparent hemophagocytic syndromes [47]. A separate group demonstrated that the anti-inflammatory molecule HO-1 is strongly associated with CD163 expression and hemophagocytosis in macrophages, and may serve a protective role in sepsis [25]. Furthermore, elevated levels of the immunomodulatory cytokine IL-10 have been identified in patients with HLH [41]. Taken together, these data beg the question of whether CD163+ erythrophagocytic macrophages actually represent an effector arm of a counterregulatory response to inflammation in the hemophagocytic syndromes [14, 15].

Natural Killer Cell and Cytotoxic CD8+ T-Cell Defects

Studies of patients with familial forms of HLH demonstrated that diminished cytotoxicity of CD8+ T cells as well as natural killer (NK) cells were central features of those disorders [48]. Subsequently, single gene defects in perforin expression were found to be causative of many cases of the familial forms of HLH [49]. Additionally, recent data have suggested that heterozygotic polymorphisms in perforin genes may be associated with the development of MAS in patients with coexistent sJIA. At

Current Pathophysiologic Understanding

Elucidation of the cytokine milieu associated with hemophagocytic syndromes, together with the identification of associated defects in T- and NK-cell cytotoxicity, have contributed to two models of the pathogenesis of MAS. In the first model, defective clearance of infected cells leads to ongoing antigen presentation by APCs, leading to dysregulated activation of T cells and macrophages and the subsequent manifestations of the disorder [54]. In the second model, defects in the cytotoxic response result in a failure to clear the APCs and activated T cells themselves, inducing the persistence of activated immune cells that would otherwise be eliminated through cytotoxic mechanisms for immune downregulation or tolerance [4, 14, 15, 54, 55]. While there is some evidence for both models, no identified infectious trigger can be found in many patients. Additionally, the finding that G-CSF worsens while cyclosporine improves the syndrome more strongly supports the second hypothesis [54].

Additional Clinical Features

Recognition of MAS in Rheumatologic Disease

The recognition of incipient MAS in patients with rheumatologic disease requires a high index of suspicion, as several characteristics of the disorder may be shared with underlying autoimmune diseases, such as cytopenia

Table 6. Presumed precipitating factors in secondary HLH

Precipitating factors	References
Medications	
Aspirin	57
Non-steroidal anti-inflammatory drugs	1, 117
Sulfasalazine	57
Etanercept	2, 3, 106
Anakinra	74
Gold salts	1, 7, 118
Morniflumate	57
Methotrexate	105, 119, 120
Infliximab	96
Penicillamine	121
Vancomycin	122
Autologous stem cell transplantation	123–125
Parenteral lipid administration	126
Infectious agents	
Epstein-Barr virus	57, 127
Cytomegalovirus	18, 19
Varicella virus	57
HHV6	128
Parvovirus B19	57
Hepatitis A	129
HIV/AIDS	33
Adenovirus	130
Coxsackievirus	57
Torovirus	44
Escherichia coli	44
Salmonella	57
Enterococcus	31
Tuberculosis	131
Visceral leishmaniasis	20, 132
Pneumocystis jiroveci	57

Table 7. Prevalence of clinical features associated with MAS complicating sJIA [1–3, 7, 8, 27, 100, 103, 117, 118, 121, 125, 133–146]

Clinical features	Patients positive, n	Prevalence in reported analyses
Fever ≥38°C	60	0.81
Hepatomegaly	45	0.61
Cutaneous rash	33	0.45
Splenomegaly	33	0.45
Hemorrhages	29	0.39
CNS dysfunction	28	0.38
Lymphadenopathy	21	0.28

and CNS dysfunction in SLE or hyperferritinemia in sJIA [23]. Furthermore, the clinical presentation of MAS may strongly resemble overwhelming infection and sepsis, the latter of which is both a more common condition and one to which patients already on immunosuppressive therapies may be predisposed [56]. The presence of factors suspected to be associated with MAS (table 6) may provide clues to the disorder, but in some cases, no antecedent trigger can be identified [57].

Therefore, while MAS should be considered in the differential diagnosis of all patients with rheumatologic disease and a change in their baseline consistent with the clinical features of the disease, the entirety of the individual clinical presentation must be taken into account in assessing the pretest probability of the disorder.

In a large review of 74 sJIA patients by Ravelli et al. [27], the onset of fever >38°C was the most common but least specific finding. However, the authors comment that the specificity data regarding fever may be misleading, as changes in the fever pattern from the spiking pattern typical of sJIA to the nonremitting pattern of MAS may provide additional information to guide the index of suspicion. The potential for clinical heterogeneity in the disorder is highlighted by the fact that less than a third of the patients in this series exhibited detectable lymphadenopathy (table 7).

Hepatomegaly was present in just over 60% of the patients with the disorder, with other features such as a cutaneous rash, bleeding diatheses, splenomegaly, and CNS dysfunction all being present in less than half of the patients. Stephan et al. [57] reported on 24 patients with a range of rheumatic diseases complicated by MAS, some of whom were included in the Ravelli series. Half of the children in their series had pulmonary involvement, and >40% required admission to the intensive care unit. Organ involvement further extended to cardiac dysfunction in 42% of patients and renal involvement in 16%.

Of the nine possible HLH-2004 criteria for MAS, three involve tests (sCD25, NK cell activity assays, and genetic testing) [58, 59] that are unlikely to be rapidly available in-house at many institutions, while a fourth requires both the ability to undergo an invasive procedure and the avoidance of sampling error [5, 27, 60]. Furthermore, even the finding of hemophagocytosis by CD163+ macrophages in marrow and other tissue is not unique to the HLH disorders [25]. Thus, routine testing of all patients with rheumatologic disease and a new clinical feature (such as fever) for each of the HLH-2004 criteria would be cost-ineffective, could confuse the diagnosis if biopsy data were misapplied in isolation, and might expose many patients to unnecessary risks. Similarly, waiting for the delayed results of HLH-2004-directed testing in pa-

Table 8. Treatment options proposed for HLH associated with autoimmune disease in case series and individual reports

Therapy	References
Cyclosporine	7, 8, 31, 57, 147
Etanercept	56, 143
Anakinra	43
Intravenous immunoglobulin	33, 75, 108, 109, 130
Etoposide	5, 60, 67, 71, 100, 148
Plasmapheresis	149
Abatacept	61
Antithymocyte globulin	7, 8, 61
Corticosteroids	7, 8, 12, 150
Naproxen	150
Splenectomy	151

tients with true MAS prior to initiating therapy could invite catastrophe [17, 23], and many patients with true MAS may require treatment initiation prior to the fulfillment of strict criteria when clinical suspicion is high [61], similar to aggressive forms of arthritis [32, 62] due to novel mechanisms [63, 64]. Lastly, differences in precipitating events, diagnostic parameters, and prognostic factors between adults and children exist [65–72], leading some authors to suggest that the current gold standard of the HLH-2004 criteria cannot be applied in the adult population [12].

Given the problems of using delayed results to diagnose a fulminant disease, together with both the poor individual sensitivity and specificity of many of the clinical findings of MAS according to the HLH-2004 criteria, certain features on routine laboratories may be of greater utility at the bedside in the initial consideration of the disorder. Indeed, the proposed Ravelli criteria for MAS complicating sJIA use laboratory values that can be quickly obtained locally at inpatient institutions with reasonably equipped laboratory facilities. However, the Ravelli criteria are to date neither validated in sJIA nor intended to apply to MAS in other disorders [20]. Furthermore, the problem of overlap of individual signs and symptoms with other rheumatologic conditions remains [27].

Grom [54] and others [23, 57, 73, 74] have suggested that the characteristically low erythrocyte sedimentation rate (ESR) in MAS may provide a valuable signal to distinguish the onset of MAS (in which the ESR falls despite worsening inflammation) from worsening of inflammation in other disorders that can be confused with MAS, but typically would manifest in the opposite change in the ESR. Ferritin, one of the HLH-2004 diagnostic criteria, is widely available in many diagnostic laboratories and has been suggested as an inexpensive first step in a diagnostic screening strategy capable of being widely applied to exclude a hemophagocytic syndrome in adult patients presenting with the systemic inflammatory response syndrome [12]. The authors propose the measurement of serum ferritin as a 'gateway' test to guide the rational application of more specialized diagnostic procedures and the rapid administration of therapy [12, 33, 75].

Treatment Considerations

No standard of care yet exists for the diagnosis and treatment of MAS in many patients with rheumatologic disease [12, 27], similar to what is observed in other forms of autoimmunity [76–78]. Case series and individual reports supporting the use of a number of immunosuppressive regimens for hemophagocytic syndromes abound in the literature (table 8).

Interpretation of the collective data is complicated by the fact that a number of the therapies described have also been implicated as potential precipitants of the hemophagocytic syndromes (table 6), and the possibility that development of presumed drug-related MAS in some patients may represent insufficient control of the underlying inflammation rather than a true drug-related event [23, 54, 79].

In 2002, Henter et al. [65] published a report demonstrating an 80% survival rate to hematopoietic stem cell transplants compared to approximately 50% survival in historical controls using the HLH-94 protocol. Building on this experience, the group [65] recently published widely accepted revised diagnostic and therapeutic guidelines for the management of children under 18 years suffering from any HLH form according to the experimental protocol of the ongoing HLH-2004 study [5, 60]. Notably, their treatment protocol recommends maximal supportive care prior to initiation of specific treatment. These measures are aggressive, and include the administration of empiric oral anti-fungal therapy, prophylactic cotrimoxazole, intravenous immunoglobulin, peptic ulcer prophylaxis, and, in patients with coexistent viral infections, consideration of specific antiviral therapy. Therapy is initiated and continued for an 8-week tapering course, with re-intensification of therapy to week-2 levels if reactivation develops (table 9).

Table 9. The HLH-2004 treatment protocol for the management of familial and secondary HLH in children younger than 18 years [5, 60]

Systemic therapy	Dexamethasone	Etoposide	Cyclosporine
Week 1	10 mg/m^2 daily	150 mg/m^2 i.v. twice weekly	3 mg/kg twice daily
Week 2	10 mg/m^2 daily	150 mg/m^2 i.v. twice weekly	dose to trough 200 μg/l
Week 3	5 mg/m^2 daily	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Week 4	5 mg/m^2 daily	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Week 5	2.5 mg/m^2 daily	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Week 6	2.5 mg/m^2 daily	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Week 7	1.25 mg/m^2 daily	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Week 8	taper and discontinue	150 mg/m^2 i.v. once weekly	dose to trough 200 μg/l
Intrathecal therapy[a]	<1 year of age	1–2 years of age	2–3 years of age
Methotrexate	6 mg	8 mg	10 mg
Prednisolone	4 mg	6 mg	8 mg

[a] CSF evaluation at diagnosis and after 14 days – if there is clinical neurologic progression or abnormal CSF at 2 weeks, intrathecal therapy should be given weekly on days 15, 22, 29, and 36.

If patients respond and there is no evidence of reactivation or a known familial HLH syndrome, a secondary form of HLH (such as autoimmune disease-associated MAS) is presumed, treatment is discontinued, and close follow-up is initiated. Where reactivation occurs or a genetic HLH syndrome is identified, continuation therapy is initiated and the patient proceeds to definitive therapy with hematopoietic stem cell transplant [5, 60].

However, application of the HLH-2004 protocol to secondary forms of HLH such as those due to malignancy or rheumatic disease may be imperfect, and the authors of the HLH-2004 guidelines concede that alternate treatment modalities may be required in these scenarios [5, 60], e.g. as many as half of the patients with MAS secondary to sJIA may respond to corticosteroids alone [23, 24, 57]. Additionally, the clinical features of MAS may differ from those seen in other forms of HLH [17, 31, 80, 81], and the features of HLH syndromes in children may differ from those in adults [12], potentially altering the risk/benefit ratio of therapies originally applied to familial and other forms of HLH.

In children, some authors have suggested risk stratification to guide approaches to initial therapy [12, 67, 71]. Similar data are not extant in adults, however [12]. Nevertheless, in both children and adults with MAS, some authors have advocated an approach centered on aggressive supportive management and high-dose corticosteroids as an initial step, followed by second-line therapies for refractory disease as indicated, such as cyclosporine A, etoposide, and the administration of intravenous immunoglobulin [12, 23]. A multinational (Canadian/Swiss/French) group has advocated an approach in adults that includes initiation of high-dose corticosteroids, elimination of known or suspected triggers, initiation of aggressive supportive measures, and infection control, with progression in the face of refractory disease to either intravenous immunoglobulin (1 g/kg for 2 days) or, in the case of malignancy or Epstein-Barr virus infection, either cyclosporine A/etoposide or appropriate chemotherapy [12]. In the event of refractory disease despite eventual progression to cyclosporine A/etoposide, the suggested protocol of Emmenegger et al. [12] allows for consideration of progression to such therapies as polychemotherapy, plasma exchange, antithymocyte globulin, splenectomy, or hematopoietic stem cell transplant.

Conclusions

MAS is a form of secondary HLH, the appropriate diagnosis and management of which have historically been clouded by an imperfect nomenclature and an immature but evolving understanding of the underlying pathophysiology. The history of the management of MAS associated with autoimmune diseases, together with associated HLH syndromes such as those that may accompany ma-

lignancy, primary immunodeficiency, and infection, highlight the critical role of the clinical immunologist at the juncture of the traditional specialties of hematology/oncology, allergy/immunology, infectious disease, rheumatology, and the subdivisions of adult and pediatric medicine thereof [82]. The modern management of MAS and other HLH syndromes has made great strides as a result of therapeutic advances over the last 20 years, similar to promising approaches to therapies [83] and etiology [84] in other clinical settings, but the promise of even greater strides looms as the benefits of standardized nomenclature, systematic investigation, and collaborative medicine take root in the soil of team-based science.

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