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REVIEW ARTICLE

A Review on Macrophage Activation Syndrome

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Abstract

MAS, which is currently grouped under secondary or acquired haemophagocytic lymphohistiocytosis (sHLH), is a rare and fatal disorder that results from excess activation of T-cells and macrophages. Though the pathogenesis of MAS is poorly understood, various proinflammatory cytokines like interleukins (IL-1, IL-6), tumor necrosis factor α (TNF α), interferons are thought to play significant roles. MAS is associated with various clinical features such as non-remitting fever, bleeding, cytopenias, splenomegaly, hepatic dysfunctions, increased levels of triglyceride, ferritin and decreased levels of albumin and fibrinogen. Early diagnosis and interventions are crucial to reduce mortality risk but diagnosis is not often easy due to persistence of wide range of features that overlap with other rheumatic diseases, most commonly sJIA (systemic juvenile idiopathic arthritis). Corticosteroids and cyclosporins are commonly used for MAS treatment. Intravenous immunoglobulins, biologic agents like IL-1 blockers (anakinra, canakinumab), IL-6 blockers (tocilizumab) are also frequently used. Moreover there is still the need of genetic and immunohistological study in order to understand the exact mechanism of the syndrome development and establishment of novel therapies with lesser toxicities.

Keywords: MAS, haemophagocytic lymphohistiocytosis, systemic juvenile idiopathic arthritis, cytokines, corticosteroids.

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INTRODUCTION

Various autoimmune and inflammatory states are known to be associated with a number of life threatening conditions. One of them is Macrophage activation syndrome[1], that is more commonly observed in rheumatic diseases such as systemic juvenile idiopathic arthritis (sJIA), Kawasaki disease, systemic lupus erythro-matosus (SLE), Still's disease, juvenile dermato-myositis and Becket's disease[2,3,4].

MAs does not hold a recent history. Familial lymphohistocytosis that shares quite similar clinical picture to MAS was first observed in 1952[5]. Later, Boone in 1976, reported MAS among the patients with compulsive coagulo-pathy and hepatic insufficiency[5] but Stephen et al was the one who coined the term Macrophage activation syndrome in 1993 and demonstrated that the excess activation of macrophages in most of his patients[6]. MAS that develops as a result of excess activation of macrophages, is emerging as a well characterized clinical facet that may be associated with different drugs, infections, cancers, hematological and rheumatic disorders or any isolated disease occurring with or without trigger[7].

Prevalence

Though a rare complication, MAS has become more common these days. In a study from tertiary care hospital about 6.7% cases of sJIA had MAS[8]. MAS is more frequently observed in children but increased prevalence is also present in adults nowadays[9]. It is a life threatening disorder with mortality rate of 20-30%[10]. Among the rheumatologic disorders, sJIA is most commonly associated with MAS[11] with the prevalence rate of 7-13%[12], but the rate may vary upto 30-40% in the unreflected cases of MAS[13]. According to Gormezano et al, MAS is also frequently associated with SLE in children with acute pancreatitis and they have higher mortality rate in comparison to those having SLE only[14].

The incidence of MAS is also high in ASOD that closely resembles sJIA. It is reported to be 7.7-16% with the mortality rate ranging between 9.5-22%[15]. The incidence of MAS in SLE is about 0.9-4.6%[16].

Features of MAS

The clinical features of MAS evolve rapidly. The common signs and symptoms presented by the patients are non-remitting high fever, hepatomegaly, splenomegaly. Neuro-psychiatric dysfunction, lymphadenopathy, pancytopenia, skin erythema, anemia and less frequent abnormalities of heart, kidneys and lung tissues[17,7,18] (Table 1).

Table 1. Signs and symptoms of MAS[20]

Features	Incidence
Fever	95%
Arthritis	64%
Hemorrhagic abnormalities	20%
Lymphadenopathy	51%
Hepatomegaly	70%
Splenomegaly	55%
Neurologic dysfunction	34%
Involvement of tissues (heart, lung, kidney)	10%

Table 2. Laboratory changes in MAS

Investigations	Changes
1. Hematological profile	
Hemoglobin	Decreases
White blood cell count	Decreases
Platelet count	Decreases
INR and PTT	Increases
ESR	Decreases
2. Biochemical profile	
Ferritin	Increases
D-dimer	Increases
Liver enzymes	Increases
LDH	Increases
TG	Increases
SCD 25 (receptor for IL-2) and SCD 163 (receptor for hemoglobin- haptoglobin complex)	Increases
Fibrinogen	Decreases
3. Histopathological changes	
Bone marrow biopsy	Increased hemophagocytic macrophages with elevations in CD163

The laboratory results in MAS are not specific, however the frequently observed changes (Table 2) are increase in hepatic enzymes, bilirubin, triglycerides, ferritin, D-dimer and lactate dehydrogenase while there is decrease in levels of sodium, hemoglobin, blood cells like leucocytes and platelets, albumin, fibrinogen, clotting factors like II, VII and X. Patients also show elevated partial thrombo-plastin time along with the presence of degradation product of fibrinogen. Levels of various cytokines are also found to be elevated. Some of the examples are interleukins (IL-1, IL-2, IL-6), tumor necrosis factor α (TNF α), interferons (INF α, INF γ) and macrophage colony stimulating factor (MCSF)[17].

Bone marrow biopsy shows the highly elevated number of well differentiated macrophages that actively phagocytize hemato-poietic cells. However hemophagocytosis may not be detectable during the initial stages and may lack sensitivity in 40% of cases[19]. Other tissues like lymph node, spleen and liver also exhibit hemophagocytic pattern but these sites are rarely explored in literatures.

Table 3. Diagnostic criteria of MAS as formulated in 2004[18]

Criterias		
1.	Molecular diagnosis having specific gene mutation consistent with HLH	
2.	Clinical and laboratory criteria (5 out of 8 are to be met→ 2 clinical and 3 laboratory)	
A.	Clinical	
	i. Fever	
	ii. Splenomegaly	
B.	Laboratory	
	i. Cytopenia	
a.	Hemoglobin (infant<4 weeks)	<9 gm/dl (adult), <10 gm/dl
b.	Platelets	<10 x 10^9/dl
c.	Neutrophils	<1 x 10^8/dl
ii.	Hypertriglyceridemia and/or hypofibrino-genemia	>265 mg/dl <0.15gm.dl
iii.	Hemophagocytosis	Bone marrow aspirate, spleen or lymph nodes
iv.	Decreased or absence of NK cell activity	
v.	Increased ferritin	->500 mg/dl
vi.	Increased soluble CD25 (Il-2 receptor)	>2400U/ml

Type of MAS

MAS is basically categorized as subtype of secondary hemophagocytic-lymphohisto-cytosis (sHLH)[21]. HLH is broadly categorized into two distinct types as:

Primary HLH (inherited or familial form)

Secondary HLH (acquired form)[19,22].

Primary HLH is autosomal recessive in nature with high incidence in infants (80% cases) compared to adults[23]. It is characterized by the following features:

Defective T-cell activation

Defective NK cell mediated cytolytic pathway

Excess production of cytokines that result in uncontrolled activation T-cells and macrophages[24].

Secondary HLH can occur at any ages due to excess immunological activation as a result of various infections caused by viruses (Epstein barr, Herpes simplex, Varicella-zoster), bacteria (Hemophilus, Mycobacterim, Brucela), fungus (candida, Histoplama), parasites (Leishmania), drugs, hematological malignancies and autoimmune inflammatory disorders[22,25].

Table 4. Diagnostic criteria for MAS complicating sJIA[7]

Criteria	Changes
A. Clinical	
1. Neurologic dysfunction	Headache, lethargy, irritability, disorientation, seizures and come
2. Hemorrhages	Purpura, ecchymoses and mucosal bleeding
3. Hepatomegaly	Liver enlargement≥3cm below coastal margin
B. Laboratory	
Decreases platelet count	≤262 x 10^6/ µl
Decreased leucocyte count	≤4 x 10^6/ µl
Decreased fibrinogen level	<250 mg/dl
Increased AST levels	>59 U/L

Table 5. EULAR/ACR criteria for MAS in sJIA

Patients with sJIA having	
1. a. Fever	
b. Increased ferritin	>684 ng/ml
2. And any two of the following criterias	
i. Platelet count	<181 x 10^9/L
ii. AST level	>48 U/L
iii. Triglyceride level	>156 mg/dl
iv. Fibrinogen level	<360 mg/dl

Diagnosis

It is often difficult and challenging to properly diagnose MAS as it can mimic infections or malignancies or may be present as the complications of sJIA. Diagnosis is also difficult in ealrly phases due to lack of pathognomic clinical findings. In 1991, the criteria for diagnosis of MAS was first proposed by a scientific team studying histocyte disorders. These criterias were later modified in 2004 [25]. According to this modified diagnostic guideline, the patient is supposed to be suffering from MAS if any one of the following characteristics is met:

Presence of gene mutations (PRF, UNC13D, STX11) associated with HLH[18] or 5 out of 8 laboratory and clinical diagnostic criterias. These include cytopenia, increased levels of triglyceride/fibrinogen, hemophagocytosis, low or absence of NK cell activity. Increase in ferritin and soluble CD25, fever and hepatospleenomegaly[21] (Table 3).

However, several researches have focused on challenges in applying 2004 diagnostic criteria for MAS, as sJIA, the most frequently associated rheumatologic disorder with MAS[26] is independently associated with hyperferritinemia, anemia[27] and leucocytosis[28] in absence of MAS. Such overlap of clinical features may pose difficulty in early diagnosis of MAS onset[29]. Likewise coagulopathies which are not only common in MAS[30] but also in other disorders can further complicate the sample collection procedure for histological diagnosis[25]. To address these issues, Raveli et al.[7] proposed a preliminary diagnostic criteria for MAS associated with sJIA in 2005. According to this guideline, diagnosis of MAS needs the fulfillment of ≥2 laboratory and ≥2 clinical criterias (Table 4).

The preliminary diagnostic guideline of Raveli et al were assessed by Davi et al, who compared it with that of 2004 diagnostic guidelines. They concluded that preliminary

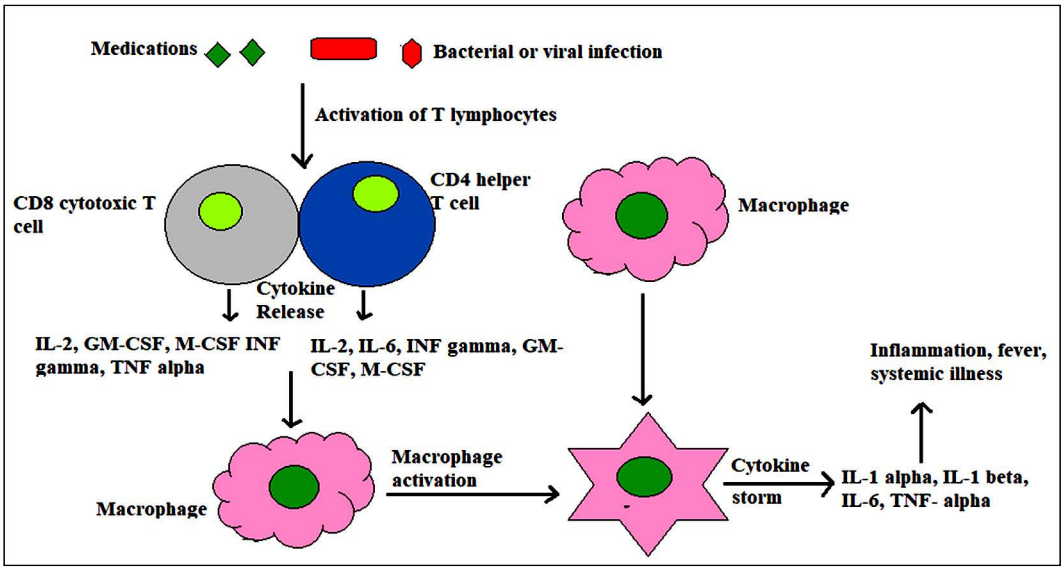

Fig. 1. Macrophage activation syndrome induced by infections and medications. Under the stimulation of bacterial, viral or fungal infection and certain medicines, T cells are activated and may directly induce apoptosis of both activated macrophages and/or T cells themselves. It results in dysregylation of cytotoxic activities causing persistent of macrophages and T cells leading to cytokine storm.

diagnostic criteria showed best results with high sensitivity and specificity of 86%[31]. Another diagnostic criteria for MAS associated with sJIA as also approved by European league agains Rheumatism/ American College of Rhematology (EULAR/ACR) in 2016 (Table 5)[32,33].

Cytokine storm in MAS

Many studies have reported high levels of cytokines, TNF receptors and IL-1R antagonists in MAS[34]. Cytokines present include proinflam-matory cytokines like those derived from lymphocytes (INF γ, IL-2) and cytokines produced by monocytes and macrophages (IL-1β, TNF γ, IL-6 and IL-18). Regulatory cytokines such as IL-10 are also elevated in MAS[34]. Patients with severe MAS may disturb the regulatory pathways of IL-10 which can lead to uncontrolled inflammation. Stimulation of toll like receptor 9 along with blockade of IL-10 receptor can lead to more severe complications[35].

IL-1α, a proinflammatory cytokine, is considered to be the central one in pathogenesis of disease. It is initially secreted in an inactive form but when cells are activated, caspase-1 protein cleaves pro IL1α to its active form. On activation, it causes further activation of lymphocytes and endothelial cells thereby stimulating production of other inflammatory cytokines like IL-6[36].

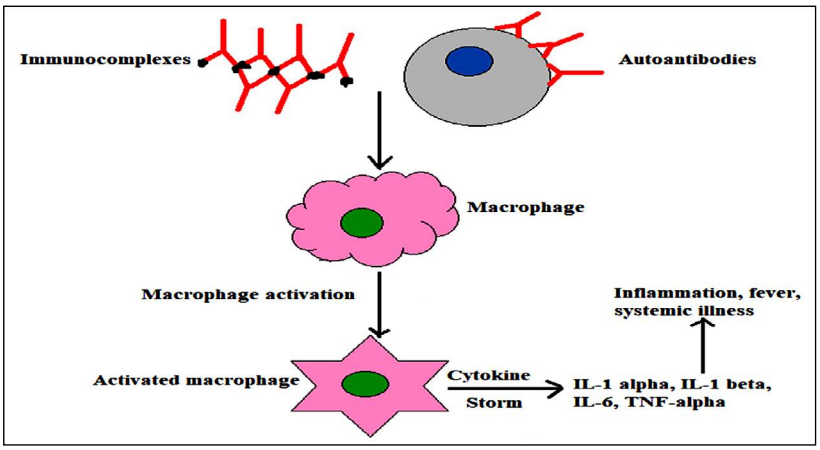

Fig. 2. Auto-antibodies or immune complexes can also stimulate macrophages resulting in production of enormous amount of cytokines

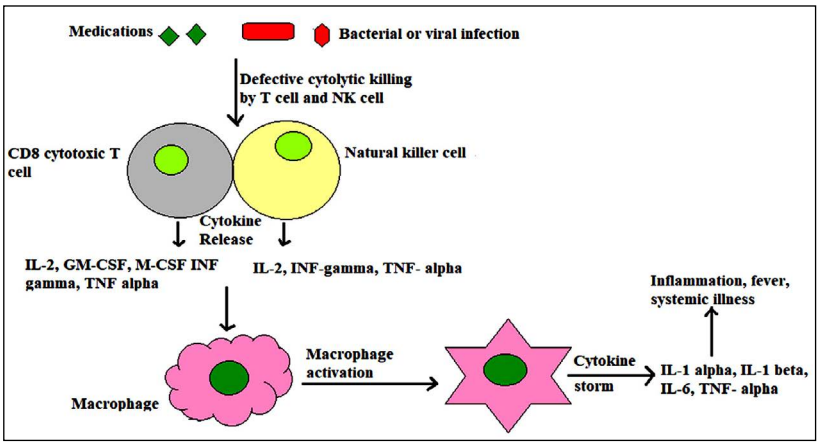

Fig. 3. Failure of cytolytic killing mechanism of T cells and NK cells due some genetic defects (such as defect in perforin gene), can also promote MAS, as defective cytotoxicity casuses continuum of antigenic stimulation leading to persistent T and NK cell activation and proliferation. Cytokines are persistently released from activated cells that further stimulate macrophages leading to cytokine storm.

Pathophysiology

The etiology and specific pathogenesis of MAS are yet to be clearly elucidated. However most of the theories derived rely on the study of primary HLH which is clinically quite similar to MAS. It is stated that hemophagocytosis can develop due to dysregulation of immunologic phenomenons resulting in the exaggeration of inflammatory responses which is characterized by excessive activation of macrophages and T lymphocytes that ultimately leads to cytokine storm[37].

It has been reported that numerous proinflammatory cytokines are released. It is also demonstrated that hyperactive T- cells and macrophages reside in various organs and produce cytokines like INF γ, TNF α, IL-6 and IL-1 which play a major role in pathogenesis of MAS. The condition is further aggravated by the presence of perforin deficiency[38]. Perforin is a type of cytotoxic protein secreted by T- cells and NK cells to destroy virus infected cells. It is also involved in regulation of lymphocyte prolife-ration. Mutation in gene coding for perforin is linked with MAS as it can lead to T-cell and NK cell dysfunction[39,40] and persistent lymphocyte activation[38].

Table 6. Major cytokines inducing MAS

Cytokines	Roles
IL-1α and	Co-stimulation of T cell
	and antigen presenting cell
IL-1β	Acute phase response
	Fever and inflammation
	Hematopoeisis
IL-2	Proliferation and activation
	of B cells, T cells and NK cells
IL-6	Proliferation pf B cell
	Acute phase response
	Stimulation of T cells
	synergistically with TNF-α
	and IL-1
INF-γ	Promotes cell mediated
	immunity
	Activates neutrophils, NK
	cells and macrophages
TNF-α	Activates signaling pathways
	that cause proliferation of
	immune cells
GM-CSF	Stimulate proliferation and
	differentiation of dendritic
	cells and
and M- CSF	monocytes

IL-1β via its receptors signals production of IL-6[41] that plays a central role in inducing acute phase response[40]. Some researchers have shown that imbalance between IL-18 and its inhibitor results in activation of macrophages and Th-1 lymphocytes that have bypassed NK cell mediated cytotoxic control, leading to the manifestation of sHLH[43-42]. IL-18 belongs to IL-1 family and stimulates the production of INF γ (by NK cells and T-cells), TNF γ and chemokines (by macrophages)[41]. The major role of INF γ is to cause profound activation of macrophages and monocytes. The increased levels of INF γ is also well correlated with clinical and laboratory features of MAS[43].

Treatment

There is necessity of urgent management of MAS. The preliminary purpose of the therapy used should be control of hyper inflammatory state with the use of immunosuppressive or cytotoxic drugs. The most commonly used drugs are corticosteroids and cyclosporins. However other therapeutic agents like etanercept, etoposide, immunoglobins in high dose and plasmapheresis are also used in practice[44].

Steroids such as methylprednisolone and dexamethasone are the first line drugs of choice as the response of patients is usually prompt. However steroids are rarely used as monotherapy for long term due to their side effects[45]. In case of MAS unresponsive to steroids alone, a combination therapy consisting of steroids and cyclosporine is given. Cyclosporin is an inhibitor of T-cell function and mostly administered in early stage of the syndrome[25]. It also has membrane stabilizing effect on macrophages[46].

Etoposide is a bone marrow suppressant and its use can result in severe infection, therefore caution is to be taken in patients having renal or hepatic impairment[47]. As per Coca et al, antithymocyte globulin (ATG) could be used in place of etoposide[48] but it may be associated with infusion reactions[49].

In case of MAS associated with sJIA, IL-1 inhibitor (such as anakinra) is being used increasingly[50]. Though the exact role of IL-1 in pathogenesis of MAS is unclear, it is expected that IL-1 inhibition may aid in better control of the disease. According to the several reports, Il-1 inhibitors have proven better treatment choice in

MAS complicating sJIA, which showed inadequate response to cyclosporins and corticosteroids[51].

Successful treatment of MAS associated with ASOD using IL-1 blockers have also been documented[46]. However according to the recent report, of 23 patients with sJIA who were treated with anakinra, one patient developed MAS[52] and in another report it was stated that anakinra might have triggered MAS in 5 out of 46 patients of sJIA[53]. IL-6 blockers (like tocilizumab) is also used as the treatment strategy among the patients who could not tolerate IL-1[46].

Activated macrophages produce IL-6 which may further amplify the macrophage response to the proinflammatory stimuli[54]. However, as per the Japaneses study, tocilizumab when used in the treatment of ASOD gradualy progressed the patient to MAS[55]. Reports regarding development of cytopenias following the use of tocilizumab in patients with sJIA (complicated with MAS) are also available[56]. Rituximab and intravenous Igs have shown satisfactory results in MAS induced by viruses like Epstein barr virus and cytomegalo virus[57].

CONCLUSION

MAS, though rare, is a potentially fatal disorder that requires prompt and appropriate treatment to prevent deleterious outcomes. Since there is lack of valid criteria for the diagnosis of MAS, the treatment appears highly variable at different clinical sectors. However the most commonly used treatment is the use of corticosteroids as monotherapy or along with cyclosporins or immunoglobulins. In some cases use of etoposide and IL-1 bockers are also recommended.

As MAS is mostly associated with rheumatic disease, clinicians should be aware of diagnostic principle and management. It is necessary to understand the underlying pathophysiology of MAS in order to identify the pathways involved in early phase of the syndrome so that better ideas could be developed in furnishing newer treatment biomarkers. Additionally larger cohorts regarding immunological and genetic studies must be carried out to formulate more effective and appropriate therapy as well as to improve mortality. Also studies have shown that the cytokine storm is the main driving force for pathology of hyper-inflammatory syndromes. Therefore therapeutic approaches blocking cytokine function might be fruitful with less toxic effects.

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CONLFICT OF INTEREST

The authors declares that there is no conflict of interest.

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