

MACROPHAGE ACTIVATION SYNDROME

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SUMMARY

Macrophage activation syndrome (MAS) is an uncommon condition in which hyperinflammation and excessive cytokine release lead to excessive stimulation of T-lymphocytes and macrophages and result in a characteristic clinical picture of haematological dysfunction and multiple organ failure. This condition occurs most commonly in the context of inflammatory conditions such as systemic juvenile idiopathic arthritis (sJIA). MAS is currently classified as one of the forms of secondary haemophagocytic lymphohistiocytosis (HLH).¹ The diagnosis of MAS is clinically important as specific therapy may be required and a missed diagnosis may lead to high mortality. Unfortunately, the diagnosis is often not easily made due to the broad range of presenting features and their overlap with other potential complications of sJIA, such as severe infection. Also, no single clinical or laboratory test is able to diagnose MAS conclusively. In this review we highlight some of the most important clinical and laboratory features, diagnostic criteria, outcomes and management of MAS.

This article has been peer reviewed.

CASE VIGNETTE

CASE 1

A five-year-old boy with known sJIA since the age of four based on polyarthritis, evanescent rash, splenomegaly, lymphadenopathy and daily fevers. Malignancy, HIV and tuberculosis were excluded at diagnosis. The patient responded well to initial therapy with corticosteroids and non-steroidal anti-inflammatory drugs and methotrexate. The patient returned to a rural area to live with his grandparents and had not been to the clinic for six months. He now presents with continuous fever, bruising, jaundice and encephalopathy as well as hepatosplenomegaly. He still has active arthritis, but his parents report that since the fevers had become more of a feature his arthritis had improved somewhat. His initial laboratory results reveal anaemia (haemoglobin 4.6 g/dl), thrombocytopenia (platelet count 50 000/ml) and leucopenia (white cell count $2.4 \times 10^3/\text{ml}$). Liver function derangement and renal failure are also present. His C-reactive protein (CRP) is 198 mg/L, but his erythrocyte sedimentation rate (ESR) is only 15 mm/hr. International normalised ratio (INR) is 3 and fibrinogen is very low. Because of a suspicion of MAS, a ferritin level of 16 400 ng/ml is detected and serum triglycerides are high. An urgent bone-marrow aspirate reveals abundant haemophagocytic macrophages, confirming the diagnosis of MAS.

EPIDEMIOLOGY

MAS is seen most frequently in children with sJIA but it is well described in other rheumatic conditions such as SLE, Kawasaki syndrome, juvenile dermatomyositis and antiphospholipid syndrome.^{2,3} It has also been described in

Adult Onset Still Disease. Episodes of MAS can complicate the course of these diseases during states of high disease activity – for example, flares or at presentation – or may be triggered by viral infections especially CMV and EBV,⁴ which are known causes of secondary HLH even in the absence of rheumatic diseases. Tuberculosis has been recognised as a trigger for MAS in countries where this disease is prevalent.^{5,6} Infections are the trigger in approximately 39 per cent of cases.⁷ Numerous medications, including sulphasalazine, gold and, more recently, some biologic agents, have in the past been implicated as triggers for MAS. It is possible that these therapies, which are now known to have no or limited value in the management of sJIA, have been implicated as bystanders in children with very severe sJIA who develop MAS as part of their sJIA.

PATHOGENESIS

The principal feature of MAS is an over-expansion and increased activity of macrophages and cytotoxic CD8+ T-cells. These cells infiltrate the bone marrow and other tissues and cause disturbance in their functioning. The normal immune response to an infection involves the recognition by dendritic cells of pathogen-associated molecular patterns (PAMPs) by toll-like receptors (TLRs). This results in an expansion of cytotoxic T-cells and macrophages by the release of pro-inflammatory cytokines such as IL-1, IL-6, IL-18 and TNFalpha. These cytokines stimulate NK cells and cytotoxic CD8+ T-cells to produce INFγ, which in turn drives the activation of more macrophages and sets up a 'cytokine storm' and a vicious cycle of cytokine release and macrophage and T-cell proliferation. The role of the activated cytotoxic cells is to clear infectious cells and to dampen the immune response

by removing dendritic cells and activated macrophages.^{8,9} This secondary self-regulatory step is crucial in titrating the activity of the immune system to the right level. Mutations in genes related to Perforin and MUNC13, which are important in mediating the granule-dependent cytotoxic effect of lymphocytes, result in familial HLH, the prototype disease for MAS. This phenomenon demonstrates the importance of this pathway in the pathogenesis of MAS.^{10,11} In active rheumatic diseases such as sJIA there is a significant increase of these cytokines as a result of the disease activity of the underlying condition.

CLINICAL FEATURES

MAS should be suspected in any child with a known rheumatic disease or features of a new diagnosis of a rheumatic disease who presents with cytopenia, liver function abnormalities and coagulopathy. It may complicate sJIA late in the clinical course or be part of the initial presentation. In younger children this makes the diagnosis more complex because HLH and other infectious and haematological causes need to be duly considered. In sJIA the pattern of fever can be an early sign of the development of MAS. In sJIA the fever pattern is very characteristically 'quotidien' – occurring daily. When this fever changes and becomes more persistently elevated, features such as infection or MAS should be considered. Additional features may include persistent rash or signs of CNS involvement such as behavioural changes or drowsiness. Ironically, joint involvement may actually lessen during MAS.

The most comprehensive study evaluating the clinical phenotype of patients with MAS secondary to sJIA described the clinical characteristics of 362 patients from 95 different investigators (which included paediatric rheumatologists and haemato-oncologists) and from 33 countries.¹² The most important clinical features and frequency of occurrence are given in Table I. In this study there were differences in presentation between patients in Europe, North America and other continents, with European patients having fewer CNS manifestations and patients from other continents having lower haemoglobin; but the overall clinical picture was remarkably similar.

LABORATORY FEATURES

MAS relies on a number of laboratory tests for its diagnosis.

TABLE I	
CLINICAL FEATURES OF MAS (%)	
Fever	96%
Hepatomegaly	70%
Arthritis	64%
Splenomegaly	55%
Lymphadenopathy	51%
CNS involvement	34%
Haemorrhagic manifestations	20%
Heart, lung or kidney failure	10%

Whereas absolute values are used in diagnostic criteria for secondary HLH and MAS, trends in the values of white cell count and platelets are essential when considering a clinical diagnosis of MAS. In a child with longstanding, active sJIA, for instance, platelet and white cell count and ESR can be markedly elevated before the onset of MAS; furthermore, a sudden drop in these values, even if not reaching the values set by diagnostic criteria, can alert the clinician to the onset of MAS and allow for timely intervention.

The relevant laboratory tests and their significance are given in Table II. In general terms, decreasing haemoglobin, leukocytes, platelets, fibrinogen and ESR as well as rising liver enzymes, INR, PTT, Ferritin, D-dimers and triglycerides herald the onset of MAS.⁴ A dramatically elevated ferritin – into the thousands (nanograms per litre) – is considered highly suggestive of MAS. This is especially so in the context of sJIA, but it is important to note that a number of other conditions can cause extremely elevated ferritin, including malignancies and chronic blood transfusions.¹³ It is also important to note that profound MAS can be present despite the absence of haemophagocytosis on bone marrow.

DIAGNOSIS AND DIAGNOSTIC CRITERIA

Much has been written about the diagnostic criteria for MAS, especially as it compares to the diagnostic criteria for secondary HLH. It is recognised that the highly inflammatory starting background disease of sJIA, with characteristically very high white cell counts and platelets, as well as relatively elevated ferritin, renders the HLH diagnostic criteria insensitive in this context. New diagnostic guidelines based on international expert consensus of paediatric rheumatologists and haematologists and on real patient data have recently been published. These are compared to the 2004 HLH criteria in Table III. In young children who present with MAS in the absence of a known rheumatic disease, differentiating from secondary HLH can be very challenging, and known HLH mutations have been described in some patients with sJIA. Protein-based and degranulation screening essays may be important in diagnosing children with primary HLH who may need more intensive therapy, including haematopoietic stem-cell transplantation.¹⁰

COMPLICATIONS AND OUTCOMES

MAS is associated with serious outcomes. The failure of multiple organ systems leads to death in approximately 8 per cent of patients and to ICU admission in approximately 35 per cent of patients.¹² Hepatomegaly, haemorrhagic manifestations, CNS dysfunction and heart, lung or kidney failure as well as lower levels of ESR, albumin and fibrinogen, and higher levels of AST, lactate dehydrogenase, triglycerides and D-dimer are associated with a more severe course.⁴

TABLE II

LABORATORY TESTS	CHANGES IN MAS
Full blood count: • Haemoglobin • White cell count • Platelets	Decreased MAS (anaemia is also a feature of sJIA) Decreased (usually high in sJIA) Decreased (usually very high in active sJIA)
Erythrocyte Sedimentation rate (ESR)	Decreases (usually elevated in active sJIA)
Liver function tests • Liver enzymes • LDH	Elevated Elevated
Clotting • INR and PTT • Fibrinogen • D-dimer	Prolonged Decreased Elevated
Ferritin	Elevated (usually extremely elevated in MAS; also high in sJIA)
Triglycerides	Elevated
Bone marrow	Shows haemophagocytic macrophages, with increased CD163 staining
sCD25 and sCD163	Elevated (not routinely available in most laboratories)

TREATMENT

SUPPORTIVE THERAPY

MAS requires urgent management. Patients may experience the failure of multiple organ systems and these complications have to be managed concurrently with

specific therapy for MAS. This may include seizure control, ventilatory support, renal replacement therapy or the provision of blood products. In conditions where MAS has been triggered by infections, these have to be managed appropriately in order for the MAS to be successfully managed and immunosuppressive or immunomodulatory agents to be safely administered.

SPECIFIC THERAPY

The evidence base for therapy in MAS in rheumatic diseases consists mostly of small case series, and the challenge of building a robust evidence base for therapy remains.¹⁶

Steroids

First-line therapy consists of high doses of corticosteroids. Methylprednisolone and dexamethasone are frequently and effectively used for this indication, usually followed by prolonged weaning using oral corticosteroids. The response to steroids is usually prompt, but steroids are seldom able to be used as monotherapy in the longer term, because their side-effect profile is unacceptable.¹²

Cyclosporin A

Usually used in combination therapy with corticosteroids, particularly in MAS, which is not steroid responsive. Cyclosporin inhibits T-cell function and is frequently used early in the course of this condition in order to allow for earlier steroid weaning.^{17,18}

TABLE III

2016 MAS DIAGNOSTIC CRITERIA (RAVELLI ET AL) ¹⁴	2004 HLH DIAGNOSTIC CRITERIA (HENTER ET AL) ¹⁵
A febrile patient with known or suspected sJIA is classified as having MAS if the following criteria are met: - Ferritin >684 ng/ml AND any two of the following: - Platelet count $\leq 181 \times 10^9/\ell$ - AST >48 units/l - Triglycerides >156 mg/dl - Fibrinogen ≤ 360 mg/dl	The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled: - A molecular diagnosis consistent with HLH - Diagnostic criteria for HLH fulfilled (five out of the eight criteria below) - Initial diagnostic criteria (to be evaluated in all HLH patients) - Fever - Splenomegaly - Cytopenias (affecting 2 of 3 lineages in the peripheral blood): - Hemoglobin <90 g/l (in infants <4 weeks: hemoglobin <100 g/l) Platelets <100 $10^9/\ell$ Neutrophils <1.0 $10^9/\ell$ - Hypertriglyceridemia and/or hypofibrinogenemia: - Fasting triglycerides 3.0 mmol/l (i.e., 265 mg/dl) Fibrinogen 1.5 g/l - Hemophagocytosis in bone marrow or spleen or lymph nodes - No evidence of malignancy - New diagnostic criteria - Low or absent NK-cell activity (according to local laboratory reference) - Ferritin 500 $\mu\text{g}/\ell$ - Soluble CD25 (i.e. soluble IL-2 receptor) $2,400$ U/ml
Comments: MAS criteria: - Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis or familial hyperlipidaemia. HLH criteria: - If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material may be obtained from other organs. Serial marrow aspirates over time may also be helpful. - The following findings may provide strong supportive evidence for the diagnosis: - spinal fluid pleocytosis (mononuclear cells) and/or elevated spinal fluid protein; - histological picture in the liver resembling chronic persistent hepatitis (biopsy). - Other abnormal clinical and laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymph node enlargement, jaundice, oedema, and skin rash. Hepatic enzyme abnormalities, hypoproteinaemia, hyponatraemia, VLDL$\uparrow$, HDL $\downarrow$.	

Etoposide

Etoposide is frequently used in primary and secondary forms of HLH and has also been successfully used in refractory cases of MAS. It forms part of the 2004 HLH treatment guidelines from the international histiocytosis society.¹⁵ Etoposide is a potent bone-marrow suppressing agent and its use may be complicated by severe infection. In addition, it is metabolised by the liver and kidney and caution is required in MAS patients with hepatic or renal impairment.

IL-1 inhibition

There is growing evidence for the use of Anakinra (IL-1 inhibitor) in the treatment of MAS complicating sJIA.¹⁹ IL-1 (or the activated form, IL-1 β) plays a central role in the pathogenesis of sJIA and a majority of patients with this condition respond to treatment with Anakinra. The mechanism by which Anakinra works in MAS is not clear, as IL-1 levels are not high in MAS.

OTHER THERAPIES

Intravenous immunoglobulin (IVIG) is not infrequently used. In fact, a recent review by Ravelli showed that it was used in nearly one-third of patients with MAS.¹²

Anakinra and IVIG are both considered relatively safe in

the face of infection and as such have an advantage over other more immunosuppressive agents.

Many other biological agents, including Tumour Necrosis Factor inhibitors, Interleukin 6 inhibitors and cytotoxic T-cell-associated protein 4 (CTLA4) antagonists have been used anecdotally to treat MAS. But there is not a strong body of evidence to support their routine use. It may be that their primary role is to treat the underlying rheumatic disease and so interrupt the cycle of inflammation.¹⁶

CONCLUSION

MAS is a relatively uncommon but life-threatening condition which occurs in children with rheumatic conditions, especially sJIA. There is some overlap between the sJIA, MAS and HLH, and genetic insights are continually increasing our understanding of the differences and similarities in these conditions. Early diagnosis and management of MAS is crucial to improving mortality. Clinicians who look after children and adolescents, especially those patients with rheumatic diseases, should be aware of MAS and the principles of diagnosis and management.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interests in relation to this publication.

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