“M” for Macrophage activation Syndrome (MAS)

What is Macrophage activation Syndrome ?

As the name suggests, MAS is a potentially life-threatening condition belonging to a group of disorders known as haemophagocytic lymphohistiocytosis (HLH). It is a condition characterized by disordered and uncontrolled activation and proliferation of T lymphocytes and macrophages due to an underlying trigger resulting in a canonical increased cytokine production and dysregulated hemophagocytosis. This results in a multisystemic inflammatory response.

Is it the same as Primary HLH? What are the triggers for MAS?

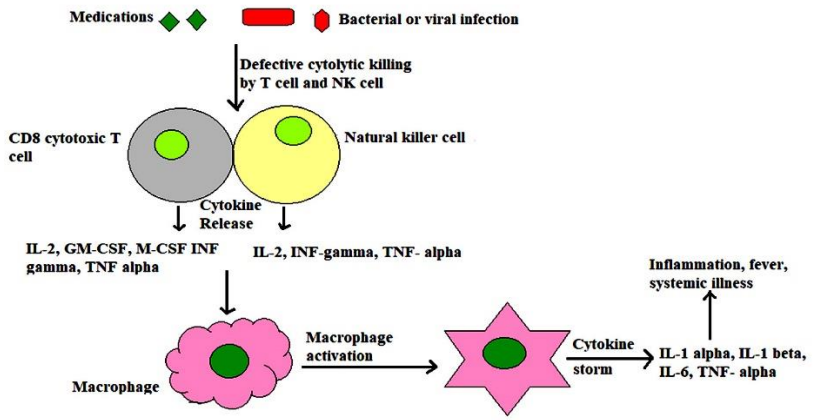
Primary or familial HLH includes patients with rare, autosomal recessive immune defects in the processing of antigens. These patients present early in life and are unlikely to survive without hematopoietic stem cell transplantation(HSCT).

Secondary HLH (sHLH) includes usually older children, in whom the condition is association with a trigger such as an identifiable infectious episode (Dengue, infectious mononucleosis, Mycoplasma infection, salmonella etc) , malignancies or an underlying autoimmune condition such as systemic juvenile idiopathic arthritis(SJIA), systemic lupus erythematosus(SLE), Kawasaki disease(KD) and Juvenile dermatomyositis (JDM).

The term “MAS” is used interchangeably by some as sHLH, whereas others reserve it to indicate hemophagocytosis secondary to an underlying autoimmune condition.

What is the pathogenesis of MAS ?

The primary trigger sets of the cytokine cascade due to uncontrolled proliferation of ill functioning cytotoxic T cells and NK cells **(Fig 1)**



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How does MAS present? When should a pediatrician think of it ?

In a backdrop of known triggers, specially autoimmune conditions(mentioned above),suspicion of MAS should be raised when encountering the following features

- High grade fever, altered sensorium, erythematous maculopapular rash, hepatosplenomegaly, lymphadenopathy are the common presenting features.
- Subtle clinical clues are in a change of fever pattern in a diagnosed case or a worsening of fever, new onset rash which is not evanescent, altered sensorium, seizures. (Specially SJIA)
- Rash might be petechial, purpuric or ecchymotic. DIC like picture might also evolve in severe cases with prolonged prothrombin time and hypofibrinogenemia as in sepsis.
- Renal dysfunction is there in some cases and mark a poorer prognosis.
- Lung parenchymal infiltrates and ARDS like presentation can also be seen.

The presentation of MAS mimics sepsis so closely that it often leads to a delay in diagnosis.

What are the laboratory parameters in MAS?

Fall in one or all cell lines is an early hallmark of MAS. Typically, platelets fall first. Early recognition of dropping counts *(albeit normal appearing should raise early suspicion specially SJIA* **(Table 1)** *)*
This occurs due to rapid destruction of phagocytes and increase consumption due to inflammation. Bone marrow aspiration shows normal to hypercellular marrow with evidence of hemophagocytosis.
ESR falls due to hypofibrinogenemia and the C reactive protein is very high.
Liver function abnormalities like transaminitis , features of coagulopathy and renal abnormality can be seen.
Another hallmark lab feature is hyperferritinemia and a ferritin value of >10,000 microliter is highly suggestive of MAS. Lastly increased LDH, Triglycerides and decreased fibrinogen complete the MAS work up . **(Table 2)**

Ferritin >684 ng/ml
and any 2 of the following:
Platelet count $\leq$181 x 10^9/liter
Aspartate aminotransferase >48 units/liter
Triglycerides >156 mg/dl
Fibrinogen $\leq$360 mg/dl

Table 1 :- MAS criteria in a setting of SJIA (considering occult/subclinical MAS, lower values but statistically significant)

Complete Blood count
ESR
CRP
SGPT,SGOT
Serum Creatinine
Serum Ferritin
Serum Fibrinogen
Serum LDH
Serum Triglycerides

Table 2. Complete MAS work up (ALL AT THE SAME TIME)

In a suspected clinical setting, recognition of anemia , leucopenia, thrombocytopenia , a very high CRP and a disproportionately low ESR with deranged coagulation profile and transaminitis are often early clues to possible MAS .

How to differentiate between sepsis, disease flare, MAS?

Early diagnosis is difficult as there are no validated diagnostic criteria.

MAS may be triggered by infections such as dengue fever, enteric fever, hepatitis A amongst other viral/bacterial infections or by a disease flare in a child with SJIA.

Impending MAS must be strongly suspected in a child with SJIA who develops persistent fevers, has a fall in ESR and a drop in platelet count associated with elevated ferritin, LDH, triglycerides and d dimers

The diagnosis of MAS must be confirmed by a bone marrow aspiration showing hemophagocytosis. Having said that , *a normal marrow **doesn't** rule out MAS .*

The value of a bone marrow lies in the virtue of it showing MAS and if not provide clues to possible triggers like an infection or an alternate etiology .

Staining the bone marrow with anti-CD 163 antibodies is helpful as the positivity of CD 163 shows expansion of highly activated histiocytes.

- In disease flare of SJIA, fever is typically 1-2 episodes (intermittent quotidian) in a day with evanescent rash, lymphadenopathy, hepatosplenomegaly. There is leucocytosis with thrombocytosis, elevated ESR and CRP along with modest elevation of ferritin.
- In sepsis , the fever is typically 3-5 episodes, there is leucocytosis with thrombocytopenia, elevated ESR and elevated CRP. There is mild elevation of ferritin.
- In MAS, the fever is remittent, high grade with fixed rash, coagulopathy. There is leucopenia, thrombocytopenia, fall in ESR, high CRP,very high ferritin usually more than 10,000 microgram/L.

The key in early diagnosis of MAS lies in a high index of suspicion, a low threshold for a complete work up and doing the full laboratory work up at the same time (since MAS is a dynamic process).

How do you treat MAS in children?

- **Glucocorticoids (GC)** are one of the main therapeutic agents for MAS and the most useful drugs for the rapid induction of remission in the setting of active disease. Intravenous pulse methylprednisolone is administered at a dose of 10-30 mg/kg (max-1 gm/dose) daily for 3-5 days, followed by oral prednisolone at 1-2mg/kg/day (max- 60mg daily) according to the severity of organ involvement.
- Early Addition of **DMARDs** (cyclosporin , biologics like Tocilizumab, Anakinra in relevant settings etc.) help control the disease activity . Occasionally HLH 2004 protocols may be used in consultation with the primary specialist.

Clinical Pearls

- ***Recognise based on clinical and suggested basic laboratory patterns***
- ***Screen using cytopenias and discrepant CRP AND ESR***
- ***Confirm using Full MAS workup. (All tests at the same time)***
- ***Document organ involvement (important from prognosis aspect)***
- ***Referral to pediatric rheumatologist (Proceed with management)***

Take home messages

- **Think of MAS to diagnose MAS -Recognition of clinical pattern crucial**
- **Inflammatory backdrop**
- **Hectic Fevers, petechial rash , organomegaly ,altered sensorium, encephalopathy often the presenting symptoms .**
- **Known triggers like infections (Intracellular infections), SJIA, KD,SLE etc often a clue**
- **Full MAS work up at the same time ideal**
- **Anemias/Cytopenias/ thrombocytopenia ,transaminitis**
- **Normal / disproportionate ESR, Elevated CRP**
- **Screen with Ferritin, fibrinogen , LDH ,Triglycerides**
- **Confirm with bone marrow (relevant settings) ,document organ involvement whilst ruling out infections /malignancies .**
- **Normal Marrow does not rule out MAS.**
- **Early referral to pediatric rheumatology care and Management in liason with the subspecialist key to successful outcomes .**

Next Coming ‘N’ for NSAIDS

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