Macrophages are important constituents of mononuclear phagocyte system, earlier known as reticulo-endothelial system. Tissue macrophages are innate immune cells with well-established roles in the primary response to pathogens, particularly abundant in capillary walls of lung (alveolar macrophages), liver (Kupffer cells), spleen, brain, connective tissues, serous cavities (peritoneal macrophages) and bone marrow. In the case of cell mediated immunity, Macrophage activating response is a T-cell mediated phenomenon resulting in activation of macrophages, capable of killing and digesting microbes. The classically known macrophage activation is induced by IFN-γ, which triggers a harsh proinflammatory response that is required to kill intracellular pathogens. Macrophages also produce pro-inflammatory cytokines: IL-1, 8, 12, TNF-α, secrete plasmin, transferrin, and cause oxidative injuries, thus contributing to the pathogenesis of various acute and chronic diseases. Macrophages play important role in immune response and autoimmune phenomenon by removing immune complexes from the circulation.

MACROPHAGE ACTIVATION SYNDROME
Is it a new entity?

Definition: It is a syndrome caused by the excessive activation and uncontrolled proliferation of T-cells and well-differentiated macrophages. This activation leads to widespread hemo-phagocytosis and cytokine overproduction, a highly stimulated but ineffective inflammatory-immune response, which can be fatal.

Macrophage Activation Syndrome (MAS) has been reported in patients with almost any rheumatic diseases and in a heterogeneous group of diseases, ranging from infections including tuberculosis to neoplasm to haematological conditions, though it is most strongly associated with Systemic Juvenile Idiopathic Arthritis (SJIA). The clinical syndrome of acute hemorrhagic, hepatic, and neurologic abnormalities in association with systemic JIA was first described by Hadchouel et al in 1985. Later on, same investigators proposed the term Macrophage Activation Syndrome (MAS), for patients having clinical features similar to the reactive hemo-phagocytic lymphohistiocytosis (HLH). In the following years, despite of a significant occurrence in adult also, this name gained acceptance in paediatric rheumatology.

Nomenclature and Classification
It is now established that Macrophage Activation Syndrome bears close resemblance to a group of histiocytic disorders collectively known as hemo-phagocytic lymphohistiocytosis (HLH). The term histiocytes refer to a group of immune cells that includes macrophages which have predominantly antigen-processing functions, and dendritic cells, which have antigen-presenting functions. Histiocytic disorders are conditions characterized by the proliferation and accumulation of macrophages and dendritic cells. The term hemophagocytosis describes the pathologic finding of activated macrophages, engulfing erythrocytes, leukocytes, platelets, and their precursor cells in bone marrow and other tissues. Hemo-phagocytic lymphohistiocytosis (HLH) is a term that describes a spectrum of disease processes characterized by accumulations of well-differentiated macrophages. In the most recent classification, these conditions are grouped under three categories:
1. Dendritic cell-related disorders,
2. Macrophage related disorders
3. Malignant disorders of histiocytes

Table I: Classification of Histiocytic disorders

<table>
<thead>
<tr>
<th>1. Dendritic-cell-related:</th>
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<tbody>
<tr>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td>Secondary dendritic cell processes</td>
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<tr>
<td>Solitary histiocytomas of various dendritic cell phenotypes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Macrophage-related:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage Activation Syndrome (MAS)</td>
</tr>
<tr>
<td>Primary hemophagocytic lymphohistiocytosis (HLH)</td>
</tr>
<tr>
<td>Secondary hemophagocytic syndromes</td>
</tr>
<tr>
<td>Infection associated</td>
</tr>
<tr>
<td>Malignancy associated</td>
</tr>
<tr>
<td>Rheumatic disease associated</td>
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</tbody>
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<table>
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<tr>
<th>3. Other:</th>
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</thead>
<tbody>
<tr>
<td>Malignant disorders</td>
</tr>
<tr>
<td>Monocyte-related</td>
</tr>
<tr>
<td>Leukemias</td>
</tr>
</tbody>
</table>

Epidemiology
Macrophage activation syndrome is a serious life-threatening complication of rheumatic diseases that, for unknown reasons, occurs much more frequently in systemic juvenile idiopathic arthritis (SJIA) and in those with adult-onset Still disease. Although considered a rare complication, macrophage activation syndrome is probably more common than previously thought. The true incidence of MAS might be much higher, since there are no validated diagnostic criteria and mild instances of MAS are not always recognized. At least 10% of the patients with SJIA develop MAS. Macrophage activation syndrome generally develops in the earlier phases of the underlying disease.3,4

Etiopathogenesis
Macrophage activation syndrome is characterized by a highly stimulated but ineffective immune response. Despite having many similarities with that of hemophagocytic lymphohistiocytosis (HLH), the exact patho-physiological relationship between MAS and HLH is not clearly understood. As HLH is not a single disease but is a hyper-inflammatory syndrome that can occur in association with various underlying genetic and acquired conditions.

The best known form is familial HLH (FHLH), which is characterized by a severe impairment of lymphocyte cytoxicity. The cytotoxic activity of natural killer (NK) and CD8+ T lymphocytes is mediated by the release of cytolytic granules, which contain perforin. The dysfunction of Natural Killer (NK) cell, is extensively explored by several researchers in MAS. Some evidence suggests that depressed NK activity, with or without abnormal perforin expression, may also be involved in the pathogenesis of SJIA-associated macrophage activation syndrome. Patients with active SJIA were found to have reduced perforin expression in NK cells and in cytotoxic CD8+ T-lymphocytes compared with patients who had other subtypes of juvenile idiopathic arthritis and healthy control subjects. NK cell dysfunction is the feature that distinguishes systemic onset JRA from other forms of JRA, and is common to the major hemophagocytic syndromes. Decreased absolute numbers of NK cells, depressed NK cell cytolytic activity, or both may be a feature that distinguishes patients with SJIA from those with other forms of juvenile idiopathic arthritis.5,6

Whether these abnormalities will help identify the disease early in the course in patients who are more prone to the occurrence of this harmful complication remains to be seen. This suggests that impaired cytotoxic functions and/or deficiency of immune-regulatory NK cells are relevant to the development of MAS. Some evidence suggests that depressed NK activity, with or without abnormal perforin expression, may also be involved in the pathogenesis of SJIA-associated macrophage activation syndrome.7,8

CLINICAL MANIFESTATIONS

Symptoms
- Headache
- Non-remitting high fever
- Increasing Pallor
- Jaundice
- Bleeding from various site
- CNS dysfunction: Lethargy, Irritability, Disorientation, Seizures, Coma

Table II: Occurrence of MAS in various Diseases

| 1. Systemic juvenile idiopathic arthritis (SJIA) |
| 2. Systemic Lupus Erythematosus (SLE) |
| 3. Polymyarticular juvenile idiopathic arthritis |
| 4. Kawasaki disease |

Precipitating Factors:
- a. Viral infections
- b. Non-steroidal anti-inflammatory drugs (NSAIDs); Aspirin
- c. Gold salts
- d. Sulfasalazine therapy
- e. Methotrexate
- f. Autologous bone marrow transplantation
Paradoxical improvement in symptoms of arthritis.

**Signs**
- Anaemia, Fever, Icterus, Generalized Lymphadenopathy, Hepatomegaly, Splenomegaly, Purpura, Mucosal bleeding, DIC

**Laboratory Findings**
1. Cytopenias: anemia, leukopenia, and thrombocytopenia
2. Abnormal Coagulation profile:
   - prolonged prothrombin time (PT)
   - prolonged partial thromboplastin time (aPTT)
   - hypofibrinogenemia, and
   - detectable fibrin degradation products (FDP)
3. Deranged Liver function Tests:
   - Increased bilirubin levels
   - Elevated alanine aminotransferase (ALT) levels
   - Elevated lactate dehydrogenase (LDH) levels
4. Hypertriglyceridemia,
5. Hyperferritinemia: elevated ferritin levels >10,000 ng/mL
6. Hyponatremia
7. Hypoalbuminimia
8. The pathognomonic feature of MAS is found in bone marrow: numerous, well-differentiated macrophages phagocytosing hematopoietic elements.

**Diagnostic Criteria**
The diagnosis of macrophage activation syndrome requires the presence of any 2 or more of the following clinical criteria or 2 or more of the following laboratory criteria or A. Clinical criteria:
- CNS dysfunction: irritability, disorientation, lethargy, headache, seizures, coma
- Hemorrhages: purpura, easy bruising, mucosal bleeding
- Hepatomegaly (≥3 cm below the costal margin)
B. Laboratory criteria
- Leucopenia (TLC < 4 x 10^9/L)
- Thrombocytopenia (Platelet count <262 x 10^9/L)
- Deranged LFT (AST > 59 U/L)
- Hypofibrinogenemia (Fibrinogen ≤ 2.5 g/L)
- Histopathologic criterion: Evidence of macrophage hemophagocytosis in the bone marrow aspirate.

**Differential Diagnosis**
Diagnosis of MAS is often difficult as it mimics:
1. Acute exacerbation of underlying JIA
2. Systemic lupus erythematosus (SLE)
3. Malignant histiocytosis (MH)
4. Sepsis
5. Visceral leishmaniasis,
6. Brucellosis
7. Tuberculosis.

**Management**
Macrophage activation syndrome (MAS) may be a life-threatening complication, all patients should be hospitalized in an ICU at a tertiary care centre. Priority should be given to obtaining central venous line access, transfusional support, and managing Sepsis which is an important complication due to the profound depression of WBCs. The abnormal coagulation profile may lead to hemorrhagic manifestations like purpura, easy bruising and mucosal bleeding. Managing hyponatremia and kidney and liver failures should be given simultaneous attention.

**METHYL PREDNISOLONE**
The treatment strategy for MAS is based on the parenteral administration of high doses of methylprednisolone. After normalization of coagulation and hematologic abnormalities, a slow taper is then performed. Frequently, MAS is resistant to corticosteroids, and cases with fatal evolutions despite the administration of massive doses of steroids have been described.

**CYCLOSPORIN**
Parenteral administration of cyclosporin A at a dosage of 2 to 8 mg/kg/d has revolutionized outcomes. There are anecdotal reports on the use of etoposide and intravenous immunoglobulins for treatment of MAS; the results conflict, and we do not suggest the use of these drugs in MAS cases.

**CONCLUSION**
MAS is a serious complication of systemic rheumatic disorders, primarily SOJIA, associated with morbidity and death. Early recognition and aggressive therapy are critical. Clinical differentiation from a typical flare of SOJIA is vital, as delay in specific therapy may prove deleterious. Further immunological and genetic studies are needed in larger cohorts of patients in order to better understand the more appropriate and effective therapy.

**REFERENCES**


