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# Macrophage activation syndrome in pediatrics: 10 years data from an Indian center

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## Abstract

**Aims:** Macrophage activation syndrome (MAS) is a dreaded complication of systemic inflammatory diseases and is most commonly seen in systemic juvenile idiopathic arthritis (sJIA). We evaluate the clinical features, laboratory findings and outcomes in pediatric MAS, assess the response to different pharmacological therapies, and finally identify possible factors associated with an unfavorable outcome.

**Methods:** This is a retrospective analysis of data from patients diagnosed as having MAS, admitted between July 2008 and April 2018 into the Department of Pediatric Rheumatology, Institute Of Child Health Kolkata. The data noted were the clinical and laboratory features, treatment details, responses to therapy and outcomes.

**Results:** Thirty-one patients were diagnosed as having MAS. Primary illness was sJIA in 26 (84%), systemic lupus erythematosus in 4 (13%) and Kawasaki disease (KD) in 1 (3%). All had fever with varying degrees of multisystemic involvement. Hyperferritinemia was universally present. Pulse methylprednisolone with cyclosporine was used for treating the majority. Ten patients (32%) expired.

**Conclusion:** Macrophage activation syndrome is a near fatal complication with protean manifestations and multiorgan dysfunction. Hyperferritinemia is characteristic, higher values being associated with increased mortality. Cases resistant to steroids and cyclosporine had a poor prognosis. Late presentations with multiorgan dysfunction were associated with the poorest outcomes.

KEYWORDS

cyclosporine, macrophage activation, methylprednisolone, systemic arthritis

## 1 | INTRODUCTION

Macrophage activation syndrome (MAS) is a potentially fatal complication of systemic inflammatory disorders first reported by Boone in 1976. In 1985, Hadchouel et al described this condition in seven patients with systemic juvenile idiopathic arthritis (sJIA). In 1992, the term "macrophage activation syndrome" was coined and Stephan et al were the first to use it in relation to juvenile arthritis. Since then, MAS has been widely described in rheumatic diseases, especially sJIA. However, it is being increasingly reported in association with systemic lupus erythematosus (SLE), Kawasaki disease (KD) and periodic fever syndromes.[1-3]

Macrophage activation syndrome is characterized by uncontrolled activation and proliferation of T cells and macrophages, leading to a storm of inflammatory cytokines. Although the incidence of MAS remains unestablished, reports show that clinically overt MAS

complicates 10% of sJIA, and another 30%-40% of children may suffer from subclinical MAS.[4] Of the total 108 children diagnosed at our center with sJIA during the study period, 26 (13.8%) developed MAS.

Prompt diagnosis and initiation of treatment is of utmost importance. We present the clinicopathological data of a series of 31 cases diagnosed as having MAS, 10 (32%) of whom succumbed.

The objective of this study was to retrospectively evaluate patients with MAS for their clinical features and laboratory findings, assess the response to treatment for different therapeutics, and possibly identify the factors responsible for an unfavorable outcome.

## 2 | MATERIALS AND METHODS

This is a retrospective analysis of data from patients diagnosed as having MAS, admitted between July 2008 and April 2018, into the Department of Pediatrics, Institute Of Child Health, Kolkata. All patients with MAS/ hemophagocytic lymphohistiocytosis (HLH) secondary to autoimmune or inflammatory connective tissue diseases were included, whereas primary HLH and HLH secondary to infections were not included. In the initial years, diagnosis was based on the HLH 2004 criteria.[5] Subsequently since 2016, following publication of diagnostic criteria for MAS in sJIA by Ravelli et al, we used these in SJIA patients.[6] The data noted were the clinical and laboratory features, treatment details, responses to therapy and outcomes.

## 3 | RESULTS

Thirty-one patients were diagnosed as having MAS. This was secondary to SJIA in 26 (84%), SLE in 4 (13%) and KD in 1 (3%). The median age at presentation was 5 years and 3 months. The male: female ratio was 1.2:1.0.

### 3.1 | Clinical features

Fever was present in all 31 cases; 84% of the children had hepatomegaly, 52% splenomegaly, 68% had a fixed rash, 65% had arthritis, 36% lymphadenopathy and 26% had bleeding manifestations. Twenty-one (68%) had central nervous system involvement manifesting as varying degrees of lethargy, drowsiness, irritability, and/ or seizures. Cardiovascular system was involved in 45% of children, presenting as myocarditis, transient coronary dilatations and 15% had pre-existing pericardial effusion. Acute kidney injury was detected in 19%, whereas 16% had pulmonary involvement presenting as acute respiratory distress syndrome and pulmonary bleeds (Table 1).

### 3.2 | Laboratory features

The mean and standard deviation of the laboratory features are described in Table 2. It is interesting to note that mean ferritin is 41 785 ng/dL but the median value stands at 21 482 ng/dL. This difference is due to the presence of very high ferritin values of >100 000 ng/dL in patients who presented late. Hypofibrinogenimia was noted in 8 of 11 patients but its surrogate marker, that is low or falling erythrocyte sedimentation rate (ESR) was seen in 21 (68%). Although 13 children (42%) had coagulopathy as evidenced by thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, only 26% had overt bleeds in the form of ecchymosis, mucosal bleeds and prolonged bleeding from venipuncture sites. Hemophagocytes were present in bone marrow of 13 (76%) of the 17 patients in whom marrow aspiration was done.

**TABLE 1** Clinical features of the study population

| Clinical feature | Total number of patients | Percentage |
|---|---|---|
| Fever | 31 | 100 |
| Hepatomegaly | 26 | 84 |
| Rash | 21 | 68 |
| Arthritis | 20 | 65 |
| Splenomegaly | 16 | 52 |
| Lymphadenopathy | 11 | 36 |
| Bleeding | 8 | 26 |
| Central nervous system involvement | 21 | 68 |
| Cardiovascular involvement | 14 | 45 |
| Renal involvement | 6 | 19 |
| Pulmonary involvement | 4 | 16 |

**TABLE 2** Laboratory findings of the study population

| | Normal values | Mean values for the study population | SD |
|---|---|---|---|
| Hemoglobin (g/dL) | 11-14.5 | 7.6 | 0.94 |
| Total leucocyte count ($\times 10^3/\mu L$) | 4.5-13.5 | 6.2 | 4.9 |
| Absolute neutrophil count | | 4104 | 3623 |
| Platelet count ($\times 10^3/\mu L$) | 150-300 | 77 | 7.95 |
| Aspartate transaminase (U/L) | 10-40 | 200 | 239 |
| C-reactive protein (mg/L) | <6 | 120 | 95 |
| Triglyceride (mg/dL) n = 21 | <150 | 343 | 144 |
| Ferritin (ng/dL) | 10-118 | 41 785 | 41 448 |
| Fibrinogen (mg/dL) n = 11 | 200-400 | 157 | 620 |
| Lactate dehydrogenase (U/L) n = 23 | 140-280 | 2124 | 1908 |

### 3.3 | Treatment and outcome

Pulse methyl prednisolone at 30 mg/kg/d for 3-5 days was used for remission induction in 29 patients (Figure 1). Cyclosporine A (CsA) 3-5 mg/kg/d was added to the ongoing steroid therapy in 15 of these patients who had inadequate clinical and biochemical response within 48 to 72 hours of initiation of steroids. Two patients of sJIA with MAS secondary to infection (chickenpox, hepatitis A) were treated with hydrocortisone. Intravenous immunoglobulin (IVIg) was used as the first drug in 5 subjects during the initial years of the study period when we were hesitant to use outright pulse steroid. Subsequently it was used as an add-on drug in four children with inadequate response to steroid and CsA, but without much success. HLH 2004 protocol (including etoposide) was used in two cases who were refractory to pulse methylprednisolone, CsA and IVIg, but both succumbed. Twenty-one (68%) patients survived but we lost 10 (32%) children. None of the patients received anakinra due to its unavailability in our country.

Two children with sJIA on tocilizumab had "silent MAS" presenting as low-grade fever and "just not feeling well", one of whom suddenly died. One child on low-dose prednisolone also presented atypically with fever but normal counts and mild CRP elevation, only to destabilize rapidly with development of severe neutropenia.

### 3.4 | Risk factors for poor outcome

Statistical analysis was done to examine the relation between hyperferritinemia and outcome. Eleven patients had ferritin >50 000 ng/mL, 8 of whom succumbed. Pearson's Chi-square test revealed a *P* value of .001 with a positive correlation (.613). Hence, hyperferritinemia >50 000 ng/mL had poor prognosis and was associated with increased mortality.

Data relating to addition of cyclosporine showed that too much dependence on steroids in the initial years of study and delay in its initiation in steroid-unresponsive patients also were associated with increased mortality.

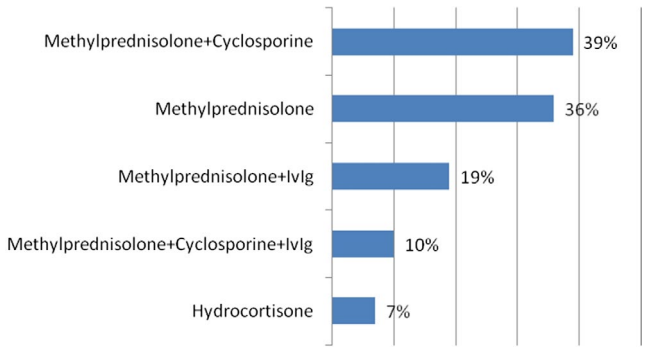


**FIGURE 1** Treatment modalities used in the study population

## 4 | DISCUSSION

Macrophage activation syndrome occurs predominantly as a complication of sJIA[7] but is being increasingly reported in association with SLE, KD[1,2] and familial Mediterranean fever.[3] In our study, sJIA was the primary illness in 84%, SLE in 13% and KD in 3%. Of the total 108 children diagnosed with sJIA in the study period, 13.8% developed MAS. The similarity of MAS with some features of sJIA disease flare makes it important to differentiate between the two. MAS is characterized by persistent fever in contrast to quotidian fever in disease flare. Other differentiating features signifying MAS are central nervous system involvement, coagulation abnormalities and thrombocytopenia, multiorgan dysfunction, pancytopenia, fall in ESR and fibrinogen, high ferritin, transaminitis, hemophagocytes in bone marrow.

Macrophage activation syndrome in SLE is more common than previously thought, with an incidence of 0.9% to 4.6%.[1] A multinational, multicentric study comprising of 38 patients with SLE and MAS was conducted and preliminary diagnostic guidelines for MAS as a complication of juvenile SLE were laid down in 2009. However, these guidelines have limitations and validation of these preliminary guidelines needs to be done.[1]

Among the 84 SLE patients presenting in the study period, 4 had MAS (4.7%). Three of these children presented with neuropsychiatric lupus flare, and 1 had refractory diffuse alveolar hemorrhage. The neurologic flare progressed to coma in 2 of the children, the onset of MAS possibly resulting in further deterioration of their mental status. Since lupus flares are also associated with cytopenias, a falling ESR, rising ferritin with development of transaminitis were the earliest predictors of MAS. There was no appreciable difference in the ferritin values from that of sJIA precipitated MAS.

The KD patient had presented late on day 14 and had already developed 2 coronary artery aneurysms. Post IVIg he had recrudescence of fever and MAS was heralded by drowsiness, increasing hepatosplenomegaly, gum bleeding and development of pancytopenia.

Macrophage activation syndrome may occur spontaneously, as a complication of active underlying disease, or may be triggered by an infection, a change in drug therapy or toxic effect of a medication. Infection is an important differential diagnosis[4] and fear of an underlying or secondary infection in a neutropenic patient with multiorgan dysfunction (MODS) always poses a threat to the treating physician. In our study infectious triggers were identified in only 2 cases (hepatitis A and varicella zoster), all others were blood culture negative without any other obvious infection. One child with sJIA developed MAS following addition of sulfasalazine at a different center. The majority developed as a consequence of active unremitting disease.

The pathogenesis of MAS is complex and multifactorial, causing a dysregulated immune response to various stimuli with consequent hypercytokinemia which is self-propagating in the absence of normal downregulation. Several genetic mutations (MUNC13-4, involving Toll-like receptor 9, Rab27aA87P, STXBP2 etc) have been implicated in the pathogenesis of HLH/MAS. They cause decreased natural killer cell activity or abnormal expression of perforin and

granyzyme which normally induce cell lysis and apoptosis, thus terminating the immune response. Low granyzyme and perforin leads to inability to terminate the immune response, leading to persistent immune stimulation and uncontrolled proliferation of macrophages and T cells.[8-10]

This leads to a constant cytokine production involving tumor necrosis factor (TNF) alpha, interleukin (IL)-1, IL-6, IL-10, and IL-18.[11] Of particular interest is IL-18 which has been recently shown to distinguish MAS from familial HLH with a 94% specificity.[12] Interferon gamma (INF) is also produced which causes conversion of macrophages to hemophagocytes. The cytokine surge together with organ infiltration by lymphocytes and histiocytes results in the characteristic clinical and laboratory findings. Patients present with high non-remitting fever due to the excess ILs, hepatosplenomegaly and lymphadenopathy because of tissue infiltration, pancytopenia secondary to the TNF and INF surge coupled with phagocytosis, low fibrinogen because of excess plasminogen activator from macrophages leading to increased plasmin which cleaves fibrinogen with consequent coagulation disorder, raised fibrin degradation products, sharply raised ferritin levels consequent to secretions from activated macrophages, raised triglycerides because of decreased lipoprotein lipase, and hemophagocytes in bone marrow.[13,14]

The majority (68%) of patients in our study had neurological involvement manifesting as lethargy, irritability, drowsiness and seizures; and this change of mental state was often the first sign of onset of MAS. This particularly applies to sJIA children who are otherwise well-looking when afebrile. A child with prolonged undiagnosed fever or a diagnosed sJIA with sudden-onset apathy or drowsiness mandates estimation of serum ferritin.

Cardiovascular involvement predominantly manifested as myocarditis. It is interesting to note that 2 children with sJIA MAS had diffuse coronary artery dilatation without any aneurysm, which normalized following successful management. Patients with pericardial effusion in sJIA were clinically observed to have higher mortality but statistical analysis could not be done because of the low number.

Presence of acute kidney injury and respiratory distress syndrome was associated with late presentation, advanced disease, higher ferritin values, steroid and cyclosporine refractoriness and had bad prognosis.

Macrophage activation syndrome is associated with significant morbidity and mortality necessitating early recognition and prompt and aggressive management. Suppression of the uncontrolled inflammation is the primary aim of therapy in MAS. Pulse therapy with intravenous methyl prednisolone at 30 mg/kg/d for 3-5 days is the commonest pharmacologic intervention for inducing remission. CsA at 3-5 mg/kg/d was added to patients who remained febrile/ drowsy after 48 to 72 hours of steroid initiation, and/ or showed persistent thrombocytopenia, neutropenia, not having at least 50% reduction in CRP and ferritin values or elevation of these values. Forty-eight percent of our cases received a combination of steroid and cyclosporine. As previously stated IVIg was administered in 29% but had debatable efficacy. In fact, the KD patient developed MAS within 48 hours of IVIg. In 2 subjects who were resistant to conventional therapy, etoposide as per HLH 2004 protocol was used; but without much success (Figure 1).

The IL-1 receptor blocking agent, anakinra is reportedly being increasingly used in MAS to achieve rapid remission when conventional therapy fails. It also helps in remission of underlying disease and therefore seems advantageous over CsA. IL-1 neutralizing antibody or soluble decoy receptors, namely canakinumab and rilonacept, respectively, have now been approved in the treatment of MAS.[15,16] Another possible advantage of such a targeted therapy is decrease in side effects related to more extensive immunosuppressive therapy. However, these agents are not widely available in every country including India and ideally their effectiveness and safety should be compared to the effects of pulse steroid therapy and/or CsA in a randomized setting. The therapeutic potential of these biologic agents in our population remains unknown.

Mortality in MAS has been reported to be around 8% in recent reports[8] but may go up to 22%.[17] Our cohort had 32% mortality predominantly associated with late presentations and consequent severe hyperferritinemia, thus underlying the importance of early diagnosis. The majority of them succumbed during the initial study period when we were over-dependent on steroids and IVIg and hesitant in adding CsA. Subsequently those with suboptimal response within 48 hours of methylprednisolone had early addition of CsA showing a significantly better response. However, five children with sJIA MAS diagnosed early were unresponsive to all available therapies in our setting and succumbed, underlining the need for newer biologics to be made available.

## 4.1 | Conclusion

Macrophage activation syndrome is a life-threatening complication of rheumatological disorders, most commonly sJIA. It has a wide array of clinical manifestations involving multiple organ systems. Patients on biologics and steroids can present with a silent MAS which may be difficult to diagnose. Hyperferritinemia is one of the hallmarks of MAS, higher levels being associated with increased mortality. Cases resistant to steroids and CsA had a poor prognosis. The mortality rate of MAS was 32% in our study which is higher than the reported statistics of 8%-22%. Late presentations with multiorgan dysfunction were associated with the poorest outcomes.

## AUTHOR CONTRIBUTIONS

PP conceived the study and drafted the manuscript. JB, MR, PPG and AN all helped in data collection and manuscript preparation. PP and PPG were involved in patient management.

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