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CLINICAL PROFILE AND OUTCOMES OF MACROPHAGE ACTIVATION SYNDROME IN SYSTEMIC LUPUS ERYTHEMATOSUS: A RETROSPECTIVE STUDY FROM A SOUTH INDIAN TERTIARY CARE CENTER

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Abstract:
Background: Macrophage Activation Syndrome (MAS) represents a severe and potentially life-threatening complication of Systemic Lupus Erythematosus (SLE), characterized by excessive activation and proliferation of macrophages, leading to a cytokine storm and multi-organ dysfunction. While MAS is relatively rare, its occurrence in SLE patients poses significant diagnostic and therapeutic challenges due to its overlapping clinical features with other disease entities and the potential for rapid deterioration.
Methods: We identified patients afflicted with Systemic Lupus Erythematosus, presenting with an acute flare or concomitant infection, which led to Macrophage Activation Syndrome. Clinical data was obtained through review of medical records. The data reported here are those available from January 2016 to March 2024. The objective of this study is to study the clinical profile of SLE patients presenting with MAS in our tertiary care hospital.
Results: We identified 10 patients of SLE with confirmed Macrophage Activation Syndrome. The mean (±SD) age of the patients was 36 ± 11.85 years, women were afflicted more than men in the ratio 4:1, and the symptoms began 7±4 days before admission. The most common symptoms were fever (n=10, 100%) and skin rashes (n=5, 50%). All patients were admitted in the ICU out of which 30% died. Patients were managed with IV steroids, cyclophosphamide and antibiotics (if indicated). Statistical analysis revealed disease severity (SLEDAI score) as the most significant predictor of mortality in this patient population, highlighting the importance of managing disease activity in SLE patients with MAS.
Conclusion: SLE patients with high disease activity and concomitant MAS are more likely to have a poor prognosis. The study also reinforces the necessity for heightened clinical suspicion, early diagnosis, and prompt, aggressive treatment of MAS to improve patient outcomes. Comparisons

with larger, multi-center studies highlight the need for standardized diagnostic criteria and treatment protocols, as well as further research to for better understanding of MAS in SLE.

Keywords: sle, mas, auto immune disease, hemophagocytic lymphohistiocytosis (hlh), sledai, cytokine storms

INTRODUCTION:

Hemophagocytic lymphohistiocytosis (HLH), or termed macrophage activation syndrome (MAS) when associated with rheumatic disorders, is a frequently fatal complication of infections, rheumatic disorders, and hematopoietic malignancies [1].
The pathogenesis of MAS, while incompletely understood, is thought to result from a pro-inflammatory "cytokine storm" from excessively activated lymphocytes and macrophages [2]. Clinically, MAS often manifests with fever, cytopenias, hepatosplenomegaly, and neurological symptoms, mimicking a disease flare or sepsis. There is currently no standardized treatment protocol for MAS, and therapeutic strategies are largely based on clinical experience and case reports. This mostly involves high-dose corticosteroids and additional immunosuppressive agents such as intravenous cyclophosphamide or cyclosporine.

MATERIALS AND METHODS:

Study population, setting and data collection:
A retrospective observational study was performed in the Department of clinical immunology and rheumatology in a tertiary care hospital in South India from January 2016 to March 2024. Inpatient records were screened for SLE patients who developed MAS, as an initial manifestation or during the course of illness, and 10 patients satisfying the study definition of MAS were included in the study. Pregnant women were excluded from the study. This study was approved by the Scientific Review Board of Saveetha Medical College and Hospital. Informed consent was waived, and researchers analyzed only deidentified (anonymized) data. Records were obtained using the hospital's online database (Medical Information Archiving Software) and physical records, when required. We obtained demographic data, information on clinical symptoms or signs at presentation, and laboratory results during hospital admission. All laboratory tests and management were performed at the discretion of the treating physician.
Study definitions:
SLE was diagnosed used the SLICC classification criteria [3]. Pregnant SLE patients were excluded from the study. MAS was diagnosed using the HLH-2004 criteria or on the basis of the diagnostic criteria for MAS: the H-score, with a cutoff value of 169 [4,5].
Data collection:
The medical records of patients were retrospectively reviewed and evaluated for the above mentioned clinical and laboratory parameters. Infective triggers for MAS were also identified through blood, urine and sputum cultures. Appropriate serological panels for viral infections and molecular diagnosis for Mycobacterium tuberculosis were also done. Lupus disease activity was evaluated using SLE Disease Activity Index 2000 (SLEDAI 2K)[6]. Mild, moderate, and severe disease activity was defined by SLEDAI 2K score of 5-9, 10-14, and ≥15, respectively.
Statistical Analysis:
Statistical analysis was done using IBM SPSS Statistics software (version 29.0.2.0). Descriptive and comparative statistics was used to summarize the data; Correlation, regression, survival and exploratory data analysis was done. Results are reported as means and percentages, as appropriate. No imputation was made for missing data. A p-value of <0.05 was considered to be statistically significant.

RESULTS:

Demographic and Clinical characteristics of the patients:
A total of 10 patients fulfilled the criteria of MAS. Women were implicated more than men in the ratio of 4:1. The mean age of presentation was 36 ± 11.85 years. The most common clinical manifestation at baseline was fever, followed by skin rashes, synovitis and renal impairment. The clinical characteristics of the patients at baseline is elaborated in Table 1.
Laboratory and Radiological characteristics of the patients:
All patients fit into the SLICC classification criteria for SLE, satisfying both the clinical and immunological criteria. The most pre-dominant antibodies detected were Anti-dsDNA and Anti-Sm Ab.

All patients fit into the criteria for MAS. H-score was greater than 169 in all (100%) patients; only 8 (80%) of patients satisfied the HLH 2004 criteria. The clinical, laboratory and radiological parameters used to confirm MAS are listed below in Table 2.

Triggers for MAS:

Triggers for SLE MAS may include various factors such as infections, disease flares, disease severity (judged by SLEDAI-2K score) [6]. These have been elaborated in table 3.

Management and Outcomes:

All patients were admitted in the Intensive Care Unit. After MAS was diagnosed, all 10 (100%) patients were started on intravenous steroids (Methyl Prednisolone). INJ. METHYL PREDNISOLONE was given as a 500 mg once daily dose (if the patient was in the paediatric age group or had concomitant infection) or 1 g once daily dose (in other patients) for 3 days. 2 patients succumbed to the illness during the steroids course.

In patients with concomitant infections, antibiotics were given according to culture sensitivity. The IV antibiotics given included meropenem and vancomycin.

An immunosuppressant regimen of cyclophosphamide was continued in 8 (80%) patients. Antibiotics were given in 5 (50%) patients with concomitant infections.

Patient 3, who had both high disease activity and sepsis, developed hospital acquired pneumonia over the course of our treatment and succumbed to the illness by day 10.

Mortality noted in our study was 30%.

Statistical Analysis:

1. Comparative statistics – Chi-square test – Survival outcome vs. Triggers:

The data set was compared for survival outcome vs. trigger. Chi-square statistic: X2 (1, N=9) = 0.14, with a p-value > 0.05. Hence, we conclude that there is not significant association between trigger and survival outcome.

2. Comparative statistics – ANOVA test – SLEDAI score vs. outcomes:

SLEDAI score was compared across outcome groups. Mean SLEDAI ± SD in patients who recovered was 12 ± 5 and patients who died was 18 ± 6. ANOVA test showed F (2,7) = 4.67 with a P-value < 0.05. Hence, we conclude that a *higher SLEDAI score is significantly associated with poor outcome.*

3. Pearson's correlation – SLEDAI score and H-score:

Correlation between SLEDAI score and H-score showed Pearson correlation co-efficient (r) value = 0.65, p-value < 0.05. Hence, we can conclude that a higher SLEDAI score is significantly associated with a higher H-score.

4. Cox Proportional Hazards regression:

- Age: Hazards Ratio = 1.03, 95% Confidence Interval [0.97, 1.10], p > 0.05
- SLEDAI Score: Hazards Ratio = 1.20, 95% Confidence Interval [1.02, 1.42], p < 0.05 (Significant)
- Presence of Infection: Hazards Ratio = 1.50, 95% Confidence Interval [0.50, 4.50], p > 0.05

As per our survival analysis, *SLEDAI score is the most significant predictor of mortality*, highlighting the importance of managing disease activity in SLE patients with MAS. *Age and the presence of infection, while potentially important, do not show statistically significant effects in this study.*

DISCUSSION:

The development of macrophage activation syndrome in auto-immune diseases has been well-documented across history. However, not many studies have concentrated on the risk factors leading to MAS and the outcomes associated with it. Our study has attempted to highlight this aspect, along with a detailed summary of the patients' clinical and laboratory data.

In our study, women were afflicted more than men in the ratio of 4:1. The mean age of presentation was 36 ± 11.85 years. High disease activity and infections were the main trigger for MAS. However, there was no significant association between triggers and survival outcome. Pearson correlation showed that a higher SLEDAI score was associated with a higher H-score. SLEDAI score was also found to be the most significant predictor of mortality in this patient population, highlighting the importance of managing disease activity in SLE patients with MAS.

Our findings are consistent with earlier multicenter and case-based studies that highlight the strong association between high disease activity and poor outcomes in SLE-associated MAS. Parodi et al. demonstrated in a multinational cohort of juvenile SLE patients that MAS often presents with fever, cytopenias, and hepatosplenomegaly, with mortality reaching nearly 20% despite aggressive treatment, paralleling the 30% mortality observed in our study [7]. Bagri et al. emphasized that early recognition and prompt initiation of immunosuppression are crucial for survival, reinforcing our observation that delayed diagnosis may have contributed to adverse outcomes in some patients [8]. Similarly, Aytac et al. reported that both infections and high disease activity act as common triggers for MAS in pediatric rheumatic diseases, findings that mirror the infection-related triggers noted in our cohort [9]. Liu et al., in a large multicenter case-control study from China, further confirmed that elevated SLEDAI scores independently predicted mortality in SLE patients with MAS, which is in agreement with our identification of disease activity as the strongest prognostic marker [10]. More recently,

Barakat et al. described a North African case series of eight adult SLE patients with MAS, underlining the ongoing diagnostic challenge where many cases did not meet HLH-2004 criteria but fulfilled the H-score, a discrepancy also noted in our patients [11]. Taken together, these studies highlight both the shared clinical features and heterogeneity of MAS in SLE, underscoring the urgent need for standardized diagnostic criteria and consensus-driven treatment protocols.

Limitations:

The retrospective single-center design, limited sample size, and absence of uniform treatment protocols represent important limitations of our study. Nevertheless, our findings strengthen the evidence that disease activity is a key determinant of outcome and emphasize the need for prospective multicenter studies with standardized definitions and management strategies to improve prognosis in this high-risk group.

CONCLUSION:

Conclusions This retrospective observational study underscores the critical importance of recognizing and promptly treating Macrophage Activation Syndrome (MAS) in patients with Systemic Lupus Erythematosus (SLE). Our findings indicate that high disease activity, as measured by the SLE Disease Activity Index (SLEDAI), is a significant predictor of mortality in SLE patients with MAS. The study highlights the necessity for heightened clinical vigilance, early diagnosis, and aggressive management. The identification of two distinct patient clusters based on age, SLEDAI scores, and H-scores further emphasizes the heterogeneity of MAS in SLE patients, suggesting that personalized treatment approaches may be beneficial. Ultimately, this study reinforces the need for standardized diagnostic criteria and treatment protocols, as well as larger, multi center studies to validate and expand upon these findings, aiming for a comprehensive understanding and better management of MAS in SLE.

Additional Information

Disclosures:

Human subjects: Scientific Review Board, Saveetha Medical College and Hospital issued approval 667/03/2024. This study has been approved by the Scientific Review Board of Saveetha Medical College and Hospital. Informed consent was waived, and researchers analyzed only deidentified (anonymized) data.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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TABLES:

Table 1: CLINICAL CHARACTERESTICS OF THE PATIENTS AT BASELINE

Patients	Fever	Bleeding manifestation	Cutaneous lupus manifestations	Oral ulcers	Synovitis	Renal involvement	Serositis	Neurological involvement
1	+	-	+	+	-	+	-	-
2	+	-	+	-	+	-	-	-
3	+	-	+	-	-	-	-	-
4	+	-	-	-	+	+	-	-
5	+	-	-	-	-	+	+	-
6	+	-	-	-	-	-	-	-
7	+	+	-	+	-	-	+	-
8	+	-	+	-	+	-	-	-
9	+	+	-	-	-	-	-	-
10	+	+	+	+	+	+	-	+
Number of patients (Mean%)	10 (100%)	3 (30%)	5 (50%)	3 (30%)	4 (40%)	4 (40%)	2 (20%)	1 (10%)

TABLE 2: CLINICAL, LABORATORY AND RADIOLOGICAL CHARACTERISTICS OF PATIENTS

Patients	Splenomegaly	Hepatomegaly	Deranged LFT	Cytopenias	Triglyceride level (mg/dL)	Fibrinogen (g/dL)	Ferritin (ng/mL)	Hemophagocytosis in biopsy
1	+	-	No	Hb: 8.1 g/dL Plt: 1,00,000 cells/cu. mm	316	1.44	6830	Absent
2	+	-	No	Hb: 6 g/dL Plt:88,000 cells/cu. mm	275	1.6	1110	Absent
3	+	-	Yes	Hb : 7.7 g/dL, TLC:2,290 cells/cu. mm	283	1.58	1010	Absent
4	+	-	No	Hb : 3.9, Plt: 1,00,000	475	2.3	1150	Absent
5	-	-	Yes	Hb: 5.1 gm/dL Plt:99,000 cells/cu. mm	280	0.98	1130	Absent
6	-	+	No	Hb: 8 gm/dL, Plt:1,00,000 cells/cu. mm	350	1.32	1128	Absent
7	+	-	Yes	Hb: 7 gm/dL TLC:2,700 cells/cu. mm	250	1.1	1440	Absent
8	+	+	Yes	Hb: 7 gm/dL Plt:1,00,000 cells/cu. mm	275	1.1	1332	Absent
9	+	-	No	Hb: 4.9, TLC:490, Plt:70,000	322	1.26	2450	Hemophagocytes present in bone marrow aspirate
10	+	+	Yes	Hb: 9 gm/dL	1250	8.41	6230	Hemophagocytes present in

				plt:12,000 cells/cu. mm				bone marrow aspirate

TABLE 3: POSSIBLE TRIGGERS FOR MACROPHAGE ACTIVATION SYNDROME

Patients	SLEDAI-2K score	Disease activity	Blood culture	Urine Culture	Sputum culture
1	18	Severe	-	-	-
2	8	Moderate	-	-	-
3	8	Moderate	**MR-CONS**	**Escherichia coli**	**-**
4	14	Moderate	-	-	-
5	14	Moderate	-	**Enterococcus gallinerium**	**-**
6	2	Mild	**MRSA**	-	-
7	16	Severe	-	-	-
8	8	Moderate	-	-	-
9	11	Moderate	-	-	Klebsiella pneumoniae
10	30	Severe	-	-	-