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Macrophage Activation Syndrome Secondary to Mixed Connective Tissue Disease: A Rare Case in a Tertiary Care Hospital of Eastern India

Jyoti Prakash[1] , Rajdeep Porel[1] , Neeraj Kumar[2], Ratnadeep Biswas[1], Vishnu S. Ojha [1]
[1]Department of General Medicine, All India Institute of Medical Sciences, Patna, Patna, IND
[2]Department of Anaesthesiology, All India Institute of Medical Sciences, Patna, Patna, IND

Corresponding author: Jyoti Prakash

Abstract:- Macrophage activation syndrome (MAS) is considered a rare, potentially fatal type of secondary hemophagocytic lymphohistiocytosis (HLH) that occurs especially in cases of rheumatic diseases. 18-year- old female presented with a history of rheumatoid arthritis who presented with fever, headache, vomiting, altered sensorium, and abnormal limb movements. She also had joint pains, alopecia, and oral ulcers.

Examination revealed neurological signs, elevated inflammatory markers, and abnormal liver function. Cerebrospinal fluid analysis showed increased protein levels. Urine analysis showed proteinuria. Anti- nuclear antibody profile indicated possible systemic lupus erythematosus (SLE) and rheumatoid arthritis. She developed aspiration pneumonitis during her hospital stay with a culture positive for Acinetobacter baumannii. A diagnosis of macrophage activation syndrome (MAS) secondary to mixed connective tissue disorder (MCTD) was made based on clinical and laboratory parameters. She was started on intravenous colistin and methylprednisolone, but unfortunately, she eventually succumbed to the overwhelming infection.

Thus, in cases of MCTD, MAS can manifest as a life-threatening condition. Therefore, it is crucial to maintain a high level of clinical suspicion for MAS in rheumatological diseases to enable early initiation of treatment with steroids or other immunomodulatory agents.

Categories: Internal Medicine, Infectious Disease, Rheumatology.

Keywords:- *Immune dysregulation syndrome, systemic lupus erythematosus, hemophagocytic lymphohistiocytosis, mixed connective tissue disease, macrophage activation syndrome.*

I. INTRODUCTION

Macrophage activation syndrome (MAS) is considered a rare, potentially fatal type of secondary hemophagocytic lymphohistiocytosis (HLH) that occurs especially in cases of rheumatic diseases [1]. The distinguishing feature of this condition involves an abnormal increase in the activation and proliferation of T cells and macrophages, resulting in elevated cytokine levels and the occurrence of hemophagocytosis. It has been associated most commonly with systemic juvenile idiopathic arthritis (SJIA), Still's disease, systemic lupus erythematosus and Kawasaki disease [2]. In this report, we present a rare case of MAS occurring in the context of mixed connective tissue disorder (MCTD), which has rarely been associated previously.

II. CASE PRESENTATION

An 18-year-old female presented with complaints of fever for two months, headache and vomiting for six days, altered sensorium for two days, and abnormal tightening of limbs for one day. The fever was low-grade (101-102°F) and associated with chills but no rigors. She had a holocranial headache and experienced three to four episodes of vomiting per day for the last six days. She had altered sensorium for two days with a reduced response to verbal commands and reduced speech output. For one day, she had episodes of abnormal body movements with tightening of all four limbs, jerky movements, tongue biting, and frothy secretions from the mouth.

Since the past two to three years, she has complained of joint pains involving multiple small joints (bilateral metacarpophalangeal joints, proximal interphalangeal joints, and wrist joints) and large joints (bilateral knee and ankle joints). The pain was worse in the mornings and resulted in restricted joint movement due to the severity, gradually resolving as the day progressed. The pain was severe enough to hamper activities of daily living. Additionally, she has experienced on and off alopecia and recurrent oral ulcers for the past two years. There was no history of any rashes. She was diagnosed as a case of rheumatoid arthritis at another facility, with rheumatoid factor levels of 90 and 78 units per milliliter on consecutive testing. Her medication history included regular intake of pain killers (non-steroidal anti-inflammatory drugs) for the last two to three years.

On examination, the patient was drowsy with a Glasgow Coma Scale score of E2V2M5. Her vitals showed a raised temperature (100.5°F) and blood pressure of 100/60 millimeters of mercury. Pallor was present.

Examination of the central nervous system revealed neck stiffness, a positive Kernig's sign, bilateral mid- dilated pupils responsive to light, increased tone of the bilateral upper limbs and the left lower limb, exaggerated deep tendon reflexes, and an extensor plantar reflex on the right side, along with an equivocal plantar reflex on the left. Higher mental functions, the rest of the motor functions, and the sensory system could not be assessed. Examination of the

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abdomen revealed hepatomegaly (felt 3 cm below the costal margin) and a just palpable spleen. On musculoskeletal system examination, no joint deformity or signs of inflammation could be noticed. No joint tenderness could be elicited. The rest of the systemic examination was unremarkable.

The differentials considered were subacute meningoencephalitis, connective tissue disorder (systemic lupus erythematosus [SLE] with neurolupus, and polyarthritis (rheumatoid arthritis).

Her blood investigations showed a hemoglobin level of 10.1 grams per deciliter, white blood cell count of 4000 cells per deciliter, platelet count of 102,000 cells per deciliter, C-reactive protein levels of 16 milligrams per liter, an erythrocyte sedimentation rate of 79 millimeters per hour, serum ferritin levels of 1650 micrograms per liter (µg/L), serum triglyceride levels of 833 milligrams per deciliter (mg/dL), fibrinogen levels of 112 mg/dL, and rheumatoid factor levels of 88 units per milliliter. The anti-cyclic citrullinated peptide levels were within normal range. The liver function test revealed aspartate aminotransferase (AST) levels of 776 units per liter (U/L), alanine aminotransferase levels (ALT) of 111 U/L, and alkaline phosphatase (ALP) levels of 405 U/L. The cerebrospinal fluid analysis showed acellular cytology, elevated protein levels of 140 mg/dL, normal glucose levels of 60 mg/dL, normal adenosine deaminase (ADA) levels of 4 international units per liter (IU/L), negative staining for specific microorganisms, sterile culture, negative results for Japanese encephalitis and Epstein-Barr virus, and equivocal results for herpes simplex virus. Additional tests revealed normal chest x-ray and electrocardiography findings, along with bilateral mild pleural effusion observed in the abdominal ultrasound. The magnetic resonance imaging (MRI) of the brain was normal (Figure 1).

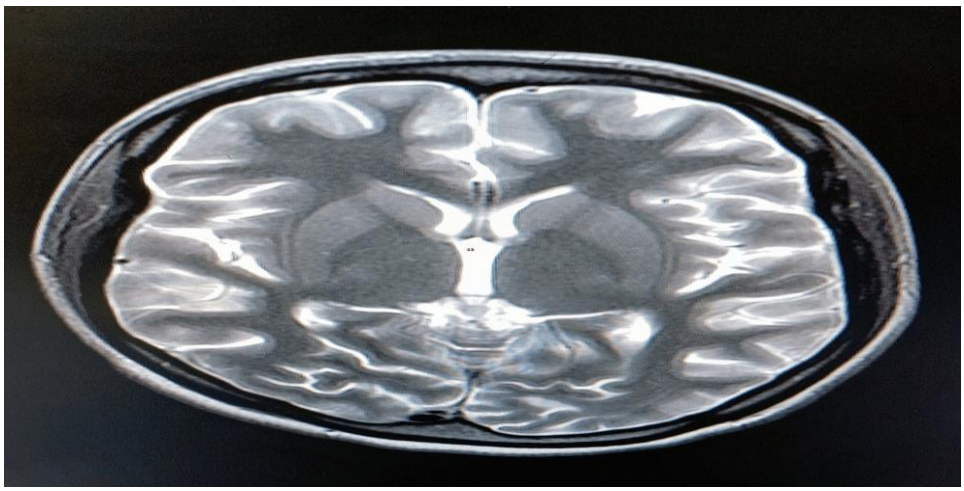

Fig. 1: Magnetic resonance imaging (MRI) of the brain showingnormal study

The patient's urine showed 2+ proteinuria. Both blood and urine cultures were sterile. The 24-hour urinary proteinuria was 632 mg/day, but urinary creatinine was three times less than normal, suggesting inadequate sampling. The anti-nuclear antibody (ANA) screening was negative but the ANA profile revealed elevated U1 RNP (3+) and Anti Ro-60 (3+), suggesting ANA-negative systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) as possible underlying conditions. Complement levels showed reduced C3 and lower side of normal C4.

During the patient's hospital stay, notable events included drowsiness and delayed arousal on day two, followed by a generalized tonic-clonic seizure and aspiration pneumonitis which evolved into acute respiratory distress syndrome (Figure 2).

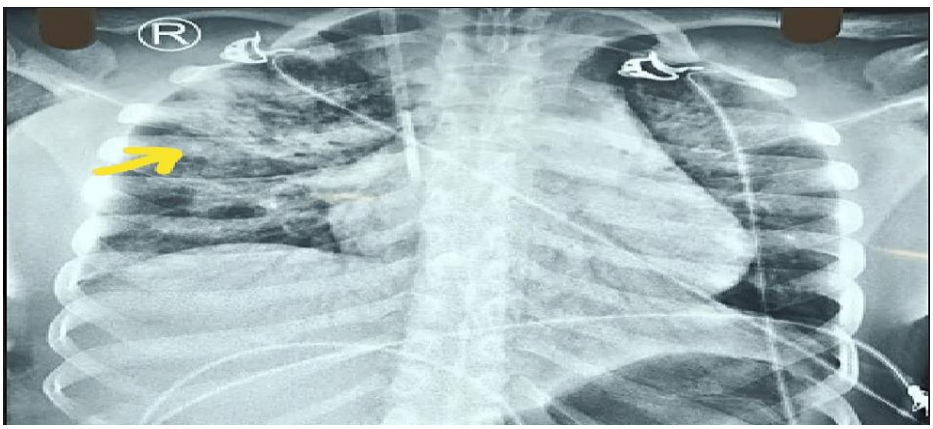

Fig. 2: Chest radiograph with the arrow pointing to consolidation in the lungs

The patient was intubated and shifted to the medical intensive care unit. On day three, a diagnosis of MAS secondary due to MCTD was made. The culture and sensitivity analysis of the endotracheal tube aspirate showed growth of Acinetobacter baumannii sensitive to colistin only. The trend of blood investigations is given in Table 1.

Table 1: Trend of blood investigations over the course of hospital stay

Parameter (unit)	Reference range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Hemoglobin (grams per deciliter)	12-16	10.1	9.5	10	8.1	8.2	7.8	8.3	9
White blood cells (cells per cubic millimeter)	4,000-10,000	4,000	10,600	9,500	4,580	8,780	6,200	6,800	20,000
Platelet count (cells per cubic millimeter)	150,000-450,000	102,000	144,000	135,000	150,000	149,000	95,000	120,000	202,000
Alanine transaminase (units per liter)	10-28	135	111	121	-	-	-	55.3	-
Aspartate transaminase (units per liter)	<31	656	776	531	-	-	-	203.5	-
Urea (milligrams per deciliter)	13-43	83	74	99	103.1	129.5	126.4	119	129.1
Creatinine (milligrams per deciliter)	0.7-1.3	1.25	1.25	1.33	1.36	1.41	1.15	1.34	1.60
C-reactive protein (milligrams per liter)	<5	16	-	40	40.6	37.9	-	196.2	193.3

The patient was started on intravenous colistin and pulse dose of methyl prednisolone. However, the patient's condition deteriorated, leading to cardiac arrest and eventual death on day eight.

III. DISCUSSION

Macrophage activation syndrome is marked by an exaggerated inflammatory response involving uncontrolled activation and proliferation of T lymphocytes and macrophages, resulting in excessive secretion of proinflammatory cytokines [3]. It closely shares its pathophysiology with HLH, and many of its clinical features, including fever, organomegaly, cytopenias, elevated triglycerides, liver dysfunction, and elevated acute-phase reactants, are thought to be caused by the cytokine storm [4]. Indeed, there is a belief that MAS is essentially synonymous with HLH. However, the term MAS is typically used specifically when it is associated with rheumatic diseases.

MAS has been commonly associated with systemic juvenile idiopathic arthritis (around 10% of patients with SJIA progress to develop evident MAS) and adult-onset Still's disease [5]. Recently other rheumatological conditions are also being implicated increasingly such as childhood-onset SLE (with incidence of nearly 10% of the patients developing MAS) [6], and Kawasaki disease (in 1-2% of the patients) [7]. It has also been reported in the background of dermatomyositis, antiphospholipid syndrome, polyarticular juvenile idiopathic arthritis, and very few cases of MCTD [8].

The HLH-2004 criteria developed by the International Histiocyte Society, are used for diagnosing cases of HLH [9]. Due to the presence of persistent fever, cytopenias, elevated levels of triglyceride and ferritin, and decreased levels of fibrinogen, the criteria were fulfilled in our case. However, the HLH-2004 criteria are often not suitable for diagnosing MAS with underlying rheumatic diseases like SJIA due to the overlap of features, such as elevated ferritin levels and splenomegaly, in active SJIA. This overlap makes it hard to distinguish MAS from a flare-up of SJIA [10], and thus, the Ravelli criteria is commonly employed for diagnosing MAS [11], and it requires fulfilling two or more laboratory criteria or any two or more clinical and/or laboratory criteria (Table 2).

Table 2: Ravelli criteria for the diagnosis of Macrophage Activation Syndrome

Laboratory criteria	Reduced platelet count (≤262,000 cells per microliter)
	Elevated aspartate aminotransferase (>59 units per liter)
	Reduced white blood count (≤4,000 cells per microliter)
	Hypofibrinogenemia (≤2.5 grams per liter)
Clinical criteria	Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
	Hemorrhages (purpura, easy bruising, mucosal bleeding)
	Hepatomegaly (≥3 centimeters below the costal margin)
The diagnosis is established when two or more laboratory criteria, or a combination of two or more clinical and/or laboratory criteria, are fulfilled.	

In this case, the presence of decreased platelet count, elevated AST levels, decreased white blood cell count, central nervous system dysfunction, and hepatomegaly, coupled with the ANA-profile, led to the diagnosis of MAS secondary to MCTD, according to the Ravelli criteria.

Our patient also fulfilled the criteria developed by Parodi et al. [12] for the preliminary diagnosis of MAS in rheumatological conditions, particularly juvenile systemic lupus erythematosus (SLE). These criteria, outlined in Table 3, can be utilized for assessment.

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Table 3: The Parodi criteria for diagnosis of macrophage activation syndrome

Clinical criteria	Fever (>38°C)
	Hepatomegaly (≥3 centimeters below the costal arch)
	Splenomegaly (≥3 centimeters below the costal arch)
	Hemorrhagic manifestations (purpura, easy bruising, or mucosal bleeding)
	Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, or coma)
Laboratory criteria	Cytopenia affecting two or more cell lineages (white blood cell count ≤4,000 cells per microliter, hemoglobin ≤9 grams per deciliter, or platelet count ≤150,000 cells per microliter)
	Elevated aspartate transaminase (>40 units per liter)
	Elevated lactate dehydrogenase (>567 units per liter)
	Hypofibrinogenemia (≤150 milligrams per deciliter)
	Hypertriglyceridemia (>178 milligrams per deciliter)
	Hyperferritinemia (>500 micrograms per liter)
Histopathological criterion	Evidence of hemophagocytosis in the bone marrow aspirate
The diagnosis of macrophage activation syndrome: at least 1 clinical criterion and at least 2 laboratory criteria. Bone marrow aspiration for evidence of macrophage hemophagocytosis may be required only in doubtful cases.	

Early detection and prompt therapeutic intervention are of utmost importance in managing MAS, a potentially fatal condition with significant mortality rates. Timely recognition of MAS symptoms and immediate initiation of appropriate treatments are essential to achieve a swift and effective response [10]. Steroids are often the first line of treatment for cases of MAS. Cyclosporine A and tumor necrosis factor alpha inhibitors have also proven quite effective in many cases [13,14]. Despite the administration of steroid therapy, our patient's condition proved fatal due to the combination of immune dysregulation leading to overwhelming sepsis and the resulting damage caused by hypercytokinemia.

IV. CONCLUSIONS

In cases of mixed connective tissue disease (MCTD), MAS can manifest as a life-threatening condition. Therefore, it is crucial to maintain a high level of clinical suspicion for MAS in rheumatological diseases to enable early initiation of treatment with steroids or other immunomodulatory agents. Given the immune dysregulation associated with MAS, the risk of overwhelming infections is increased, necessitating aggressive antimicrobial therapy.

ADDITIONAL INFORMATION DISCLOSURES

- **Human subjects:** All authors have confirmed that this study did not involve human participants 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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