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Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) Evolving into Macrophage Activation Syndrome (MAS) in a Child with Pyrexia of Unknown Origin

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Abstract

Macrophage activation syndrome is a potentially life-threatening complication of rheumatic diseases. Here, we report the case of a 4-year-old boy who presented with fever for 5 months, initially moderate-high grade, abdominal pain for 3 months, and pain in BL knee and ankle joints for 2 months. On examination, the child had multiple cervical lymphadenopathies and no organomegaly. The differential of disseminated tuberculosis, lymphoma, and juvenile idiopathic arthritis. The initial blood count was normal. The Chest X-Ray was also normal. Bone marrow examination showed normal hematopoiesis. The excisional biopsy of the cervical lymph node showed reactive lymphadenitis. During the course of hospitalization, the patient developed high-grade fever with hepatosplenomegaly and swelling of BL ankle and knee joints. The blood count at 2 weeks suggested pancytopenia, and liver function test indicated increased aspartate aminotransferase. Chest X-Ray showed BL pleural effusion, a clear transudative fluid was aspirated. C-Reactive protein, serum ferritin, and triglycerides were raised, and his bone marrow exhibited hemophagocytosis, while the Erythrocyte sedimentation rate and fibrinogen levels were decreased. Based on ILAR (International league against Rheumatism's) and PRINTO (Paediatric Rheumatology International Trials Organisations) criteria, a diagnosis of Systemic onset juvenile rheumatic arthritis with macrophage activation syndrome was made. The patient was managed with intravenous methylprednisolone, intravenous immunoglobulin, and tacrolimus. The patient showed gradual clinical improvement and was discharged on clinical improvement and was doing well on follow-up at 4 weeks and 6 months.

Keywords: MAS • SOJIA • Hemophagocytosis • HLH

Introduction

With death rates as high as 53%, macrophage activation syndrome is one of the deadliest complications of juvenile inflammatory disorders. Early diagnosis and treatment are essential for better outcomes. Given that systemic onset juvenile rheumatic arthritis (SOJIA) exhibits significant inflammatory manifestations, identifying macrophage activation syndrome in SOJIA may be challenging. Supportive therapy, which includes proper nutrition and calorie intake, hydration, electrolyte management, intravenous corticosteroids, intravenous immunoglobulins, and long-term immunosuppressants is the cornerstone of care in children [1-6]. The case we present here exhibited hepatosplenomegaly, lymphadenopathy with pleural effusion, elevated inflammatory markers and liver enzymes, thrombocytopenia, and reduced fibrinogen and ESR during the course of hospitalization, and promptly responded to treatment, unlike most cases. We present the case of a previously healthy preteen male who presented to the tertiary care centre in Northern India. (May 2022 to December 2022).

Case Presentation

A previously healthy preteen male reported a history of fever for 5 months which was intermittent, moderate-high grade, no aggravating factor and relieved on medication, abdominal pain for 3 months, and pain in BL knee and ankle joints for 2 months. There was a history of significant weight loss of 5% over 3 months as reported by the parents. On examination, the child was afebrile and had multiple significant cervical lymphadenopathies with no organomegaly. There was no swelling of the knee and ankle joint on inspection, no tenderness on palpation of the knee and ankle joint and no decrease in range of motion, and no local rise of temperature. The patient was managed as a case of PUO and a differential diagnosis of disseminated tuberculosis, lymphoma, and juvenile idiopathic arthritis was kept.

During the course of hospitalization over the next 2 weeks, the patient developed high-grade fever (documented up to 105'F), with a progressive increase in the size and the number of lymph nodes (maximum diameter of 2 x 2cm). On examination, he was febrile and tachycardia (HR-160/min) was present. However, the BP was within the 50th and 95th centile (92/60mmHg), pulses palpable, and peripheries were warm. There was severe pallor and swelling, pain, and increased temperature of BL ankle and knee joints. There were multiple petechiae in B/L lower limbs. He also developed hepatosplenomegaly (Liver 3 cm BCM and spleen 5 cm BCM). Nosocomial infections were ruled out by sending a blood and urine culture and testing for malaria, dengue, and leptospirosis. All the reports were negative. A CBC was sent which was suggestive of pancytopenia. Repeat LFT was s/o elevated SGOT/SGPT, and inflammatory markers were raised. There was clinical and laboratory suspicion for systemic onset juvenile idiopathic arthritis with macrophage activation syndrome (Figure 1).

Investigation

Initial tests revealed hemoglobin of 8.1g/dl, TLC of 15200cells/mm3 (N76L20E2M1), and a platelet count of 4.47lacs/mm^3 which later decreased to 5g/dl, 3639cells/mm^3 (N55L40E1M1), and 40,000/mm^3 respectively. At presentation, serum urea was 17.3mg/dL and serum creatinine 0.56mg/dL, C-reactive protein (CRP) 79.73mg/dL, erythrocyte sedimentation rate (ESR) 100mm in 1st hour initially which reduced to 30mm during the course

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of hospitalization. Also, at two weeks of hospitalization, fibrinogen levels of 199mg/dL, ferritin levels of 100,000mg/dL, and triglyceride levels of 287.2mg/dL were measured in serum. The Liver function test showed SGOT of 233.8IU/L and SGPT of 61IU/L and S.LDH of 2877IU/L. The initial chest X-ray was normal (Figure 1); however, a repeat chest X-ray showed the presence of BL pleural effusion (Figure 2). Clear pleural fluid was tapped, and routine microscopy showed a transudative picture and the culture was sterile. The patient was also investigated for tuberculosis as per the NTEP (National Tuberculosis Elimination Programme) protocol, the chest X-ray was not suggestive of TB; negative results for Acid fast bacilli and CBNAAT were obtained from a gastric aspirate [7]. The excisional biopsy of the enlarged cervical lymph nodes was done to rule out lymphoma, which was suggestive of reactive lymphadenitis. S.ANA and Rheumatoid factor were negative. Bone marrow aspiration and biopsy done initially were suggestive of normal haematopoiesis. During the course of hospitalization, the patient developed a high-grade fever; thus, blood and urine cultures were sent to rule out nosocomial infection; however, both cultures were negative. IgM dengue, IgM scrub typhus, and IgM Leptospira were also negative. EBV DNA RTPCR was also done which was negative. IgM CMV, CMV DNA, and Parvo B19 DNA RTPCR were sent which were negative. 2D ECHO was done to rule out infective endocarditis and it turned out normal. Repeat bone marrow was suggestive of hemophagocytosis. The PRINTO criteria for SOJIA with MAS were fulfilled. Prior to discharge, repeat inflammatory markers were assayed and ferritin was lowered to 6928.3mg/dL, triglycerides were 186 mg/dL, CRP was 40mg/L, and the ESR was 50mm in the 1st hour (Table 1).

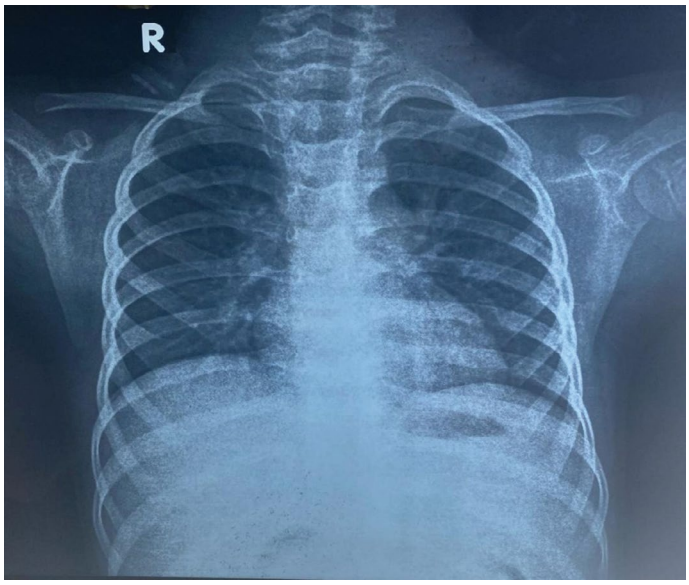

Figure 1. Chest X-Rays at the time of admission.

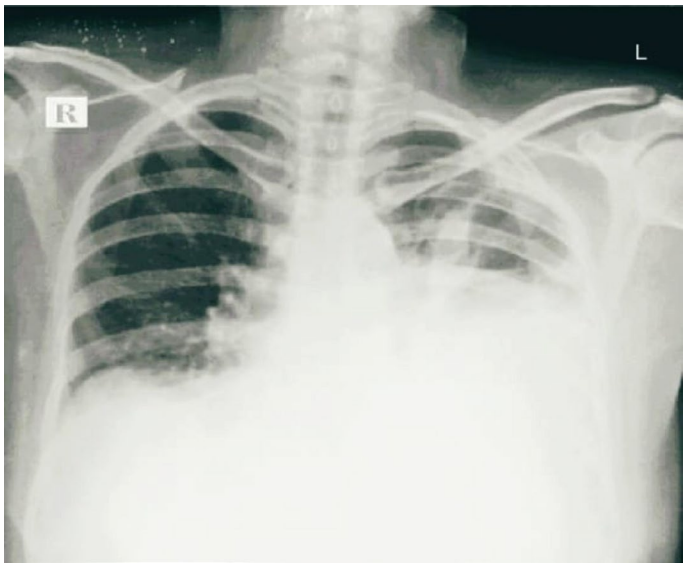

Figure 2. Chest X-Rays during hospitalisation showing BL pleural effusion.

Differential diagnosis

At the time of admission, on the basis of history, clinical examination, and laboratory findings a differential diagnosis of disseminated tuberculosis, lymphoma, and juvenile idiopathic arthritis was kept. The chest X-Ray was done which was normal. Gastric aspirate for AFB and CBNAAT was negative. S.ANA was negative. The FNAC from LN was inconclusive. excisional LN biopsy was performed which was suggestive of reactive lymphadenitis. IgM EBV and EBV DNA RTPCR were negative. IgM Parvo B19 and IgM CMV were negative. Parvo B19 DNA PCR and CMV DNA PCR were negative. Initially, bone marrow was suggestive of normal haematopoiesis. CBC was suggestive of microcytic hypochromic anaemia and leucocytosis with neutrophilic predominance.

During the course of hospitalization over 2 weeks, the patient developed high-grade fever, with a progressive increase in the size and the number of lymph nodes, hepatosplenomegaly, swelling of BL ankle and knee joints, and multiple petechiae in BL lower limbs.

Nosocomial infections were ruled out by sterile blood and urine cultures and negative tests for malaria, dengue, and Leptospira. A repeat CBC was sent which was suggestive of pancytopenia. Repeat LFT was s/o elevated SGOT/SGPT. X-Ray chest was suggestive of BL pleural effusion. On pleural tap, a clear transudative fluid was obtained which was sterile on culture; CBNAAT for TB was also negative. A normal 2D ECHO and ASO titre values ruled out endocarditis and rheumatic fever.

All this led to a strong suspicion of SOJIA with MAS. ESR, CRP, and Ferritin levels were sent, and a repeat bone marrow was done which showed hemophagocytosis. The peripheral smear also showed the presence of mild hemophagocytosis. Serum ferritin was 100,000 ng/ml. ESR which was initially 100mm in 1st hour, dropped to 30mm and CRP was 110mg/dl. CBC showed microcytic hypochromic anaemia with leukopenia and thrombocytopenia with elevated LDH. Serum triglycerides 298mg/dl and fibrinogen was 140mg/dl. A normal fundus examination ruled out uveitis. Therefore, a diagnosis of SOJIA with MAS was made [2-4].

Treatment

The patient presented as a case of pyrexia of unknown origin. The relevant investigations were sent, and empirical antibiotics ceftriaxone and amikacin were started. The patient was orally allowed. During the course of hospitalization, the patient had a persistent high-grade fever and oral intake decreased to negligible and hence the patient was started on intravenous fluids, oxygen support, and antibiotics were upgraded to ceftriaxone and

Table 1. Investigations during hospitalisation.

	Day 1	Day 5	Day 7	Day 14	Day 21	Day 28
Hb (gm/dl)	8.1	8.2	7.8	5	9.68	10.8
TLC (cells/mm^3)	15200	19200	9600	3639	8687	9700
DLC	N76L20	N72L24	N40L42	N55L40	N56L40	N70L26
Platelet (lac/mm^3)	4.47	3.8	1.6	40,000	52,000	1.79
Ferritin (ug/ml)		-	-	100000	-	6928.3
CRP (mg/dl)	54.21	-	-	79.73	-	40
ESR (mm in 1sthour)	-	-	100	30	-	50
S.triglycerides(mg/dl)	-	-	-	287.2	-	186
S.Fibrinogen	-	-	-	199	-	-
SGOT (IU/L)	49.9	-	-	233.8	-	163.1
SGPT (IU/L)	22.7	-	-	61	-	27.2
Bone Marrow	-	Normal	-	Haemo Phagocytosis	-	-
S.Uric acid (mg/dl)	5.28	-	-	-	-	-
S.phosphorus (mg/L)	3.74	-	-	-	-	-
S.Na (mmol/L)	136.5	-	-	129	-	136
S.Albumin (gm/dl)	3.54	-	-	2.41	-	-

vancomycin according to institutional protocol.

After the patient satisfied the ILAR and PRINTO criteria for SOJIA with MAS, according to the HLH 2014 protocol the patient was started on pulse methylprednisolone therapy (30mg/kg/day) for 5 days and IVIG (total dose-2 gm/kg in 2 divided doses) was given on days 4 and 5 @1gm/kg/day. He was given naproxen (10mg/kg/day in 2 divided doses) for arthralgia. The patient was started on tab prednisolone (2mg/kg/day) for 2 weeks followed by tapering doses over the next 6 weeks and Tacrolimus at 0.15mg/kg/day for 1 year. As per HLH 2014 protocol treatment with etoposide was planned in case of further deterioration [2-6].

Results

Outcome and follow up

Following treatment for SOJIA with MAS, the patient's condition gradually improved. He was weaned off oxygen within 2 days, afebrile and hemodynamically stable with no evidence of respiratory distress and he began taking well orally. Repeat investigations were sent which showed a decreasing trend of the inflammatory markers. At discharge, a repeat Chest X-ray figure 3 demonstrated the resolution of pleural effusion. The patient had no new complaints on follow-up after 2 weeks. Since the patient did not have any joint pain on follow-up, tab naproxen was stopped, and oral prednisolone was continued in tapering doses along with tab tacrolimus. Repeat follow-up was done after 1 month. The patient was afebrile, hemodynamically stable, was able to interact well with friends and family, and resumed school. The serum tacrolimus levels were done on follow-up. It was 5.58ng/ml (therapeutic range-5-10ng/dl), hence tacrolimus was continued in the same dose.

The patient was followed up after 2 months, and there were no fresh complaints. Complete blood count and inflammatory markers were repeated at 6 months follow up- Hb-14.8gm/dl, TLC- 14690 cells/mm^3, Platelet- 3.9lac/mm^3, creatinine-0.44mg/dl, SGOT-40IU/l, Na- 142mmol/L, CRP<0.5mg/dl and Ferritin 320ug/L. S. tacrolimus levels were 3.8ng/ml, hence it was continued at the same dose. HbA1C was done which was 3.7 at 6 months follow-up.

Discussion

Systemic onset JIA (SOJIA) is a distinctive subtype of juvenile idiopathic arthritis (JIA) which is a systemic arthritis subtype according to the ILAR classification (International League of Associations for Rheumatology) [2]. The clinical definition includes the 2-week duration of fever and arthritis along with any 1 of the following – hepatosplenomegaly, lymphadenopathy, serositis, and typical evanescent rash [2]. Diagnosis is based on the identification of clinical criteria and exclusion of conditions like malignancy and infection.

Macrophage activation syndrome is a rare and potentially life-threatening complication of children with SOJIA. The clinical pointers to diagnosis hepatosplenomegaly, hemorrhages, and central nervous system dysfunction (Figure 2) [3,4].

Hong Shi, et al. observed the development of MAS in 13 of 90 (14.4%) patients admitted with SOJIA [7-9]. All the patients with MAS had a high-grade fever; 12 (92.3%) had hepatomegaly; 10 (76.9%) had coagulopathy, and 8 patients (61.5%) had central nervous system dysfunction. All patients had rapid onset thrombocytopenia, leukopenia, and a decrease in ESR with an increase in inflammatory markers.

Manoj A, et al. reported a similar case of a 4-year-old girl who presented with fever and pain in BL shoulder and hip joint for more than 2 weeks [10]. The initial fever workup was negative, and she was started on empirical antibiotics and discharged on clinical improvement. Two weeks later, she presented with a high-grade fever, rash, irritability, breathlessness, and abdominal distension. She had hepatosplenomegaly and pancytopenia with reduced ESR. On further evaluation, she also fulfilled the criteria for SOJIA with MAS and improved clinically on immunosuppressive therapy.

Kumar S, et al. reported a case of a 6-year-old managed as a case of PUO. 2D ECHO was suggestive of dilated coronary vessels so the patient was managed as incomplete Kawasaki disease and given IVIG with no clinical improvement [11]. There was progressive clinical deterioration, and the patient was intubated and kept on mechanical ventilation. Subsequently, on further clinical and laboratory evaluation the patient fulfilled HLH-2004 criteria and he was diagnosed with macrophage activation syndrome. He finally responded when he was administered cyclosporine and etoposide in addition to dexamethasone (HLH-2004 protocol).

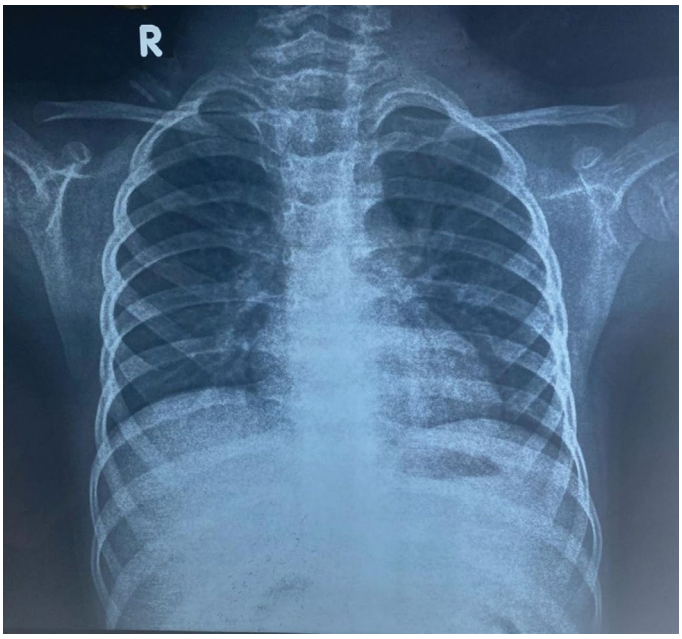

Figure 3. Chest X-Rays at discharge.

Similar to our patient who was also deteriorating during the course of hospitalization and promptly reported to the HLH 2014 protocol for MAS. Juneja M, et al. reported a case of a 12-year-old diagnosed case of SOJIA with sudden onset fever, abdominal distension with severe pallor, lymphadenopathy, and severe anaemia [12,13]. In view of the presence of hepatosplenomegaly, pancytopenia, and worsening of the mental status possibility of MAS was considered and steroids were started. The patient had a further worsening sensorium and died on the same day. Bone marrow aspiration later revealed macrophages phagocytosing hematopoietic elements (Table 2).

In our case, initially, the diagnosis of SOJIA was missed as there was no quotidian fever, rash, and no organomegaly. The diagnosis of MAS was delayed as the patient did not have any CNS symptoms and bleeding manifestations early in the course of the disease.

The preliminary diagnostic guidelines for MAS in sJIA provided by Ravelli, et al are increasingly used and were proved to perform best in diagnosing MAS in sJIA in a retrospectively evaluated cohort of 362 MAS patients and 749 disease controls in a study conducted by Devi S, et al. (Table 3) [14-16].

A crucial goal of the PRINTO alliance was to establish a unique set of diagnostic guidelines *via* a multi-step procedure. A questionnaire with 28 clinical, laboratory and histopathological characteristics was distributed to 505 pediatric rheumatologists worldwide, and the results were used to identify potential diagnostic criteria [17]. A new set of (laboratory) diagnostic criteria to identify MAS in sJIA from MAS was proposed by PRINTO in 2015, in part based on the findings of this questionnaire (Table 4).

Patient perspective (Patient's father)

I had seen many physicians before admitting my son to this hospital since he had a high-grade fever that was not going down despite my best efforts and therapy. Doctors began injectables and oral medication for my kid after he was hospitalized, and several blood tests were done. Naproxen pill alleviated joint discomfort. However, none of it was particularly helpful, and the majority of the issues were not improving. The majority of the tests, including the bone

Table 2. Review of literature.

Author	Year	Study Design	Subject	Result and Conclusion
Ravelli, et al. [2]	2005	Comparative study	74	The preliminary clinical and laboratory criteria of MAS in SJIA were formulated
Hong Shi, et al. [9]	2006	Retrospective study	13 of 90 patients of SOJIA (14.4%)	Most common clinical manifestation of MAS- Fever>hepatomegaly> coagulopathy> CNS dysfunction
Juneja M, et al. [12]	2009	Case report	1	Delay in the diagnosis of MAS in SOJIA can lead to adverse outcomes and increased mortality
Kumar S, et al. [11]	2010	Case report	1	MAS in SOJIA can present with coronary vessel dilation and present as incomplete Kawasaki disease
Minoia et al. [13]	2014	Descriptive study	362	Decreased platelet count, increased AST, triglycerides, ferritin, and LDH were common laboratory findings.
Manoj A et al. [10]	2015	Case report	1	SOJIA with MAS presenting with clinical deterioration following discharge.
V Boom et al. [14]	2015	Systematic review	27 papers were included: 7 on diagnosis, 9 on biomarkers, and 11 on treatment	MAS has almost no validated diagnostic criteria. Ravelli criterion with. Ferritin fared well.PRINTO had introduced a unique set of diagnostic criteria to identify.MAS from active sJIA and infection.
Lerkvaleekeel B et al. [8]	2018	Literature review		Early diagnosis and prompt initial treatment are both key factors for a favorable outcome in MAS.

Table 3. Criteria to diagnose MAS as per rivelli et al.

Clinical Criteria
Central nervous system dysfunction
Haemorrhages
Hepatomegaly
Laboratory Criteria
Decreased platelet count (<262x 10^9/L)
Elevated level of aspartate aminotransferase (>59IU/L)
Decreased WBC count (< 4x10^9/L)
Hypofibrinogenemia (<2.5g/dl)
The presence of 2 or more laboratory or any 2 or more clinical and laboratory criteria is required

Table 4. Printo criteria for MAS (Paedatric Rheumatology International Trials Organisations).

A patient with suspected SOJIA with MAS [2]
Fever and serum ferritin >684ng/ml
AND any 2 of the following
Platelet count ≤181 x10^9/L
Aspartate aminotransferase > 48IU/L
Triglycerides >156mg/dl
Fibrinogen ≤360mg/dl
Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidaemias.

marrow examination, were normal and unhelpful.

After two weeks, my kid began to suffer breathing difficulties, as well as little red rashes on both legs and feet; an X-ray of the chest was performed. Doctors told me that there was an accumulation of fluid in his chest, as well as that his liver and spleen were growing in size; this worried me and my family. We also looked on the internet, which stated that it may be cancer or some other life-threatening ailment.

Doctors ran more tests and told me that my kid has a kind of arthritis in young people as well as a serious related condition. The bone marrow test was redone. Doctors told me that their suspected diagnosis was right and that the bone marrow testing indicated MAS disease. Treatment for this condition began. The sickness seemed to have stopped after two days of IVIG therapy. I was able to notice a considerable improvement in his health after five days of methylprednisolone injection.

Some blood tests and a chest X-ray were redone, and the results suggest a significant improvement, including the resolution of fluid collection in the chest. His symptoms had subsided, and physicians informed me that he was about to be discharged.

For the first time in a long time, my kid felt better. Doctors briefed me about the condition, its origin, chronic course, and potential consequences. A detailed account of each occurrence was supplied at the time of discharge, and I was instructed to follow up on a regular basis. Doctors, especially senior doctors, were always extremely kind, and I was constantly kept up to date on the next course of action, including all potential diagnoses, by the doctors.

Conclusion

The diagnosis of SOJIA is mainly clinical and based on the ILAR criteria. The diagnosis of MAS is based on the PRINTO criteria and involves a combination of clinical and laboratory criteria. Clinical presentation of MAS involves sudden clinical deterioration with persistent high-grade fever and a rise in inflammatory markers with a fall in ESR, fibrinogen, and platelet. High degree of clinical suspicion is warranted as MAS is inadvertently fatal with a high risk of mortality if undiagnosed. Prompt diagnosis and aggressive management are essential for good outcomes.

Conflict of Interest

The authors declare no conflicts of interest. The following case report is ethically approved by the institutional ethical committee.

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