Macrophage Activation Syndrome as Presenting Manifestation in Systemic Lupus Erythematosus: A Case Report

Kristine Dominique T. Padiernos, MD,[1] Rodeo V. Navarroza, MD,[2] Jeremias T. Balgua, Jr, MD,[3] and Rico Paolo Tee, MD,[4]

Abstract

Introduction. Macrophage Activation Syndrome (MAS) is a rare but life threatening pro-inflammatory complication of multiple autoimmune diseases leading to cytokine storm. We report a case of MAS as a presenting manifestation of Systemic Lupus Erythematosus.

Case Report. A 32-year-old female, newly diagnosed with Systemic Lupus Erythematosus (SLE), presents with a 3-month history of fever and joint pains, which began a few days after receiving her first dose of a viral vector COVID-19 vaccine. She later developed facial edema, and her fever became persistent and unremitting. Upon presentation, she was initially hypotensive, tachycardic, with distended neck veins, with periorbital edema and muffled heart sounds. Initial work-up revealed pericardial effusion, anemia, thrombocytopenia, elevated creatinine, hypoalbuminemia, hematuria, and pyuria. She was intubated, started on inotrope, and underwent pericardiocentesis. Patient was classified as SLE based on Systemic Lupus International Collaborating Clinics Classification (SLICC) Criteria despite negative antinuclear antibody (ANA). Nevertheless, she was started on IV steroids and hydroxychloroquine. She was eventually extubated after significant clinical improvement. Further work-up for MAS was however done due to persistent febrile episodes. Hyperferritinemia, hypertriglyceridemia, hypercholesterolemia, pancytopenia, transaminitis, and splenomegaly on imaging were noted. She was then started on methylprednisolone pulse therapy. After treatment, marked clinical improvement, as well as resolution of transaminitis and pancytopenia were noted.

Conclusion. A high index of suspicion for MAS should exist in a patient with pyrexia of unknown origin with concomitant autoimmune disease. In this disease that can lead to progressive organ failure, early diagnosis and management is crucial. This case report culminates the need for diagnostic and therapeutic guidelines that will help in the early diagnosis and immediate treatment of this debilitating condition.

Keywords Hemophagocytic lymphohistiocytosis, Hemophagocytic Syndrome Diagnostic Score, Macrophage Activation Syndrome, Systemic Lupus Erythematosus, Autoimmune disease

Introduction

Hemophagocytic lymphohistiocytosis (HLH) or Macrophage Activation Syndrome (MAS) is an infrequent yet potentially life-threatening complication that can arise in the context of various autoimmune disorders.[1] This is an inflammatory state marked by impairments in the cytotoxic functions of NK cells and CD8 T-cells, resulting in insufficient induction of apoptotic cell death. This leads to prolonged activation of T lymphocytes and macrophages, subsequently causing an excessive production of pro-inflammatory cytokines.[2,3]

[1] Diplomate in Internal Medicine, Ospital ng Muntinlupa
[2] Consultant, Section of Rheumatology
[3] Consultant, Section of Cardiology
[4] Consultant, Section of Hematology
Corresponding author: Kristine Dominique T. Padiernos, MD Email:

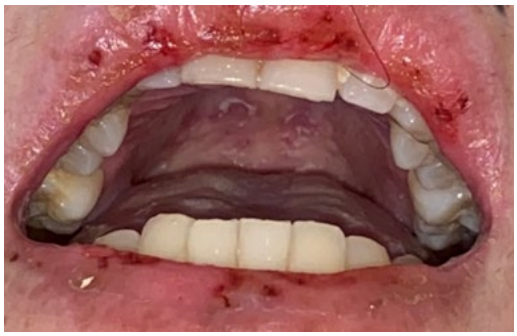

Figure 1. Oral aphthoid lesion in SLE

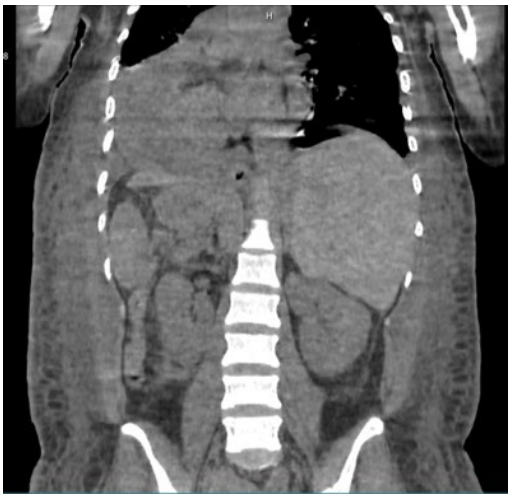

Figure 2. WAB CT SCAN showing splenomegaly

Table I. Initial Complete Blood Count at Presentation

	Actual Value	Reference Range
Hemoglobin	123 g/L	125-169 g/L
Hematocrit	35	38-50
White Blood Cell	4.4	5-10 x 10^9 g/L
Platelet	67	150-350 x 10^9 g/L
Neutrophil	0.69	0.40-0.60
Lymphocyte	0.21	0.20-0.40
Monocyte	0.09	0.02-0.08

Table II. Basic Blood Chemistry Results Upon Presentation

	Actual Value	Reference Range
ESR	38 mm/hr	0-20 mm/hr
LDH	798.3 U/L	140-280 U/L
Ferritin	>1000 ng/mL	12-150 ng/mL
AST	254.4U/L	8-33 U/L
Triglycerides	585.84 mg/dL	<150 mg/dl

Table III. Pericardial Fluid Analysis

	Actual Value
Color	Dark Yellow
Transparency	Turbid
WBC	0.013 X 10^9 /L
RBC	0.006 X 10^{12} /L
Neutrophils	0.54
Lymphocytes	0.46
Glucose	4.68 mmol/L
Protein	41 mg/L
LDH	33.5 u/L

We present a case of SLE initially presenting with MAS. This case clearly illustrates the diagnostic difficulty of identification of MAS, a condition that is under-recognized but carries a very high risk of morbidity and mortality. Our purpose is to present the features of MAS and distinguish it from SLE.

Case Presentation

A 32-yr old Filipino female overseas worker based in Riyadh, with no known co-morbidities, non-smoker, non-alcoholic, no illicit drug use, with only two male lifetime sexual partner, no heredofamilial disease, presented with a 3-month history of fever and joint pains, which she noted a few days after receiving a viral vector COVID-19 vaccine. Fever was intermittent, with a maximum body temperature reaching 40°C, spiking 3-4 times daily. Joint pains involved both hands and knees, with no apparent swelling. She also had episodes of exertional dyspnea and easy fatigability.

One month prior to admission, she developed facial swelling and periorbital edema. Fever became persistent and unrelieved by paracetamol. She decided to return to the Philippines to seek medical care. While on quarantine, intermittent fever episodes recurred with a maximum body temperature of 40°C. This was accompanied by oral ulcers (see *Figure 1*), tea-colored urine and loose watery stools. Patient did not seek consult and no medications were taken. Upon completion of quarantine, her dyspnea worsened. She consulted in our institution wherein she was noted to be hypotensive with a BP of 80/60 mmHg, tachycardic at 110 bpm, with periorbital edema, distended neck veins, crackles mid to base of right lung field, muffled heart sounds and grade 1 bipedal edema. Which prompted her subsequent admission.

Initial workup revealed cardiomegaly on chest radiography. Echocardiography showed massive pericardial effusion with signs of tamponade physiology. Prothrombin time, partial thromboplastin time were prolonged, and blood urea nitrogen and creatinine were elevated. There was also hyponatremia, hypoalbuminemia, and hypocalcemia. Patient was started on intravenous electrolyte correction and BENEPROTEIN® on diet. Peripheral blood count (see *Table I*) revealed leukopenia (white blood cell count [WBC] 4,400 x 10^6/uL) and thrombocytopenia (platelet count of 67,000/uL), with normal hemoglobin level (123 g/L). There were also noted elevations of erythrocyte sedimentation rate (ESR 38 mm/hr) and lactate dehydrogenase (LDH 798.3 U/L) (*Table II*). Thyroid-stimulating hormone TSH and C-reactive protein were within normal, and Anti-Streptolysin O titer was negative. Urinalysis revealed proteinuria (+3), bilirubinuria (+1), pyuria (WBC 10-15/hpf) and hematuria (Red Blood Cells

Table IV. Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus in our patient

Criteria Fullfilled by patient

CLINICAL CRITERIA

1. *Oral ulcer on hard palate*
2. *Serositis (pericardial effusion)*
3. *Leukopenia (WBC 3.13 x **10^6/uL)***
4. *Thrombocytopenia (platelet of 37,000**/uL)***

IMMUNOLOGIC CRITERIA

1. *Low complement low C3*

Table V. Systemic Lupus Erythematosus Disease Activity Index 2000 in our patient

Parameter	*Patient's score*
Seizure	0
Psychosis	0
Organic brain syndrome	0
Visual disturbance	0
Cranial nerve disorders	0
Lupus headache	0
CVA	0
Vasculitis	0
Arthritis	0
Myositis	0
Urinary casts	0
Hematuria	4
Proteinuria	4
Pyuria	4
Rash	0
Alopecia	0
Mucosal ulcers	2
Pleurisy	0
Pericarditis	2
Low complement	2
Increased DNA binding	0
Fever	1
Thrombocytopenia	1
Leukopenia	1
TOTAL	**21 points**

[RBC] 50-55/hpf). *Entamoeba histolytica* cysts were seen in stool exam hence was started on Metronidazole 500mg tab q8. COVID-19 Reverse transcription polymerase chain reaction (RT PCR) nasopharyngeal swab test was negative.

She was started on dobutamine drip and underwent pericardiocentesis. The pericardial fluid analysis (see *Table III*) revealed a dark yellow turbid fluid, WBC count of 0.013 x 10^9/L, RBC count 0.006 x 10^{12}/L, 54% neutrophils and 46% lymphocytes with mature blood elements, and no acid-fast bacilli (AFB). She was subsequently hooked to mechanical ventilation due to acute respiratory failure. ANA was negative, while complement component 3 (C3) level was low. She was classified as SLE based on the 2012 SLICC Criteria with a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 21 (see *Tables IV and V*).[26] Hydrocortisone 100 mg IV was given every 8 hours, and hydroxychloroquine 200mg 1 tablet daily was started. Patient was extubated the next hospital day and her blood pressure was eventually stabilized without the need for inotropes.

On the fourth hospital day, she was noted to be confused and disoriented. Pancytopenia was noted on repeat peripheral blood count. Due to the persistent febrile episodes with maximum temperature of 39.5°C, infection work-up was done and broad-spectrum antibiotics were started. Blood and urine cultures were negative for bacteria. Sputum as well as pericardial fluid were both negative for AFB and aerobic bacteria. Procalcitonin was not elevated.

High-grade fever persisted despite antibiotic therapy, hence work-up for MAS was done. Serum ferritin (>1000 µg/ml), triglycerides (585.84 mg/dL) and aspartate aminotransferase (AST) (254.4 U/L) were all elevated. Direct and indirect Coomb's test were negative. She was with pancytopenia with a hemoglobin of 90, WBC of 3.13 and platelet of 37,000/uL. Splenomegaly was noted on whole abdominal CT (*Figure 2*). Hemophagocytic Syndrome Diagnostic Score (H score) (see *Table VI*) was 207, indicating 88% to 93% high probability of MAS. Methylprednisolone 500 mg IV was given for 3 days. She responded well to the regimen with noted resolution of fever, pancytopenia and transaminitis. After 23 days of being admitted, she was discharged after marked clinical improvement.

Discussion

New-onset autoimmune manifestations following COVID-19 vaccination were reported by. Chen et al. citing instances of newly emerging autoimmune conditions after COVID-19 vaccination. These occurrences are linked to several key mechanisms: molecular mimicry, antibody production, and the influence of specific vaccine adjuvants. In their research, they also documented three case reports in which individuals were diagnosed with systemic lupus erythematosus (SLE) after exhibiting SLE-like symptoms following COVID-19 vaccination.[17] Our patient initially presented the first symptom of fever and joint pains after COVID-19 vaccination three months preceding consult.

ANA serves as the distinctive immunological marker for systemic SLE.[13] Since ANAs were first identified in SLE patients, these antibodies have been regarded as a crucial, if not consistently present, immunological indicator. Consequently, the existence of ANAs has been included as a criterion in the classification of individuals with SLE, whether following the American College of Rheumatology (ACR) or the SLICC criteria set.[14] Our patient satisfied four clinical criteria and one immunologic criterion of the SLICC classification criteria for SLE, namely oral ulcers, serositis (pericardial effusion), leukopenia, thrombocytopenia, and low complement levels. However, we were not able to apply the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for

Systemic Lupus Erythematosus (EULAR/ACR) criteria (see *Table VII*) because of the negative ANA. The SLICC-2012 and EULAR/ACR-2019 criteria both demonstrated sensitivities of 91.3% and 88.6%, along with specificities

Table VI. H Score for macrophage activation syndrome in our patient

PARAMETER	*OUR PATIENT*	*H Score*
Known underlying immunosuppresion	None	0
Temperature (°C)	Persistent fever with maximum temperature39.5°C (day 11)	49
Organomegaly	Splenomegaly on abdominal CT scan	23
No. of cytopenias	Hemoglobin 9g/dL, platelet 37,000/uL, wbc 3.13 x 10^6/uL (day 11)	34
Ferritin (ng/ml)	>1,000	0
Triglyceride (mmoles/liter)	Triglyceride 585.84 mg/dL	64
Fibrinogen (gm/liter)	Not done	0
Serum glutamic oxaloacetic transaminase (IU/liter)	AST 254.4 U/L (day 1)	19
Hemophagocytosis features on bone marrow aspirate	Not done	0

Table VII. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

ENTRY CRITERION
ANA at a titer of ≥ 1:80 on Hep-2 cells or an equivalent positive test (ever)

Criteria not fulfilled by patient

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

ADDITIVE CRITERIA
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion n at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score.

CLINICAL DOMAINS AND CRITERIA	Weight	**IMMUNOLOGY DOMAINS AND CRITERIA**	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Hematologic		**Complement proteins.**	
Leukopenia	3	Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4	**SLE-specific antibodies**	
Neuropsychiatric		Anti-dsDNA antibody* OR Anti-Smith antibody	6
Delirium	2		
Psychosis	3		
Seizure	5		
Mucocutaneous			
Non-scarring alopecia Oral ulcers	2		
Subacute cutaneous OR discoid lupus	2		
Acute cutaneous lupus	4		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total Score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

SOURCE: Aringer, M., Costenbader, K., Daikh, D., Brinks, R., Mosca, M., Ramsey-Goldman, R., Smolen, J. S., Wofsy, D., Boumpas, D. T., Kamen, D. L., Jayne, D., Cervera, R., Costedoat-Chalumeau, N., Diamond, B., Gladman, D. D., Hahn, B., Hiepe, F., Jacobsen, S., Khanna, D., & Lerstrøm, K. (2019). 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis & Rheumatology, 71(9), 1400–1412. https://doi.org/10.1002/art.40930

of 93.8% and 97.3%, respectively.[12] The 2019 EULAR/ACR classification criteria for SLE necessitated the presence of a positive ANA result as a mandatory entry criterion, at least on one occasion.[10] Nonetheless, in a recent investigation conducted by Choi et al, it was found that in individuals newly diagnosed with SLE, 6.2% of patients tested negative for anti-cellular antibodies.[11] Additionally, research has revealed that up to 30% of individuals with SLE, who undergo screening for participation in clinical trials evaluating new therapies, tested negative for ANA. Consequently, data from clinical trials suggests the presence of either previously unrecognized limitations in ANA testing assays or the possibility that some patients may transition into a serologically negative state.[13]

A significant quantity of case reports has detailed instances of protein-losing enteropathy (PLE) associated with SLE. PLE is an uncommon manifestation of SLE distinguished by low serum albumin levels and clinical symptoms encompassing edema, heightened vulnerability to infections, and serositis.[18] In a case-control study conducted by Chen et al., it was observed that 27.3% of patients with PLE exhibited isolated GI involvement as their primary presentation of SLE. These individuals displayed hypoalbuminemia, hypocalcemia, elevated cholesterol levels, and reduced levels of complement proteins C3 and C4. Additionally, 23% of these patients tested positive for anti-dsDNA antibodies.[23] Our patient presented with diarrhea with associated hypocalcemia, hypoalbuminemia, hypercholesterolemia, serositis, and edema, features characterized in SLE-related PLE.

El-Badawy and colleagues illustrated the correlation between hyponatremia and elevated SLEDAI scores, increased ESR, heightened C-reactive protein levels, higher anti-dsDNA titers, and the presence of reduced complement levels in individuals with SLE.[20] Furthermore, they deduced that hyponatremia in individuals with SLE is closely linked to heightened inflammation. Swart and colleagues also clarified that IL-6, a pivotal proinflammatory cytokine, functions as a locally produced secondary messenger within signaling pathways activated by lipopolysaccharides. It serves as an effector in specific brain regions responsible for vasopressin release.[21] The patient presented with hyponatremia that persisted during hospitalization. Furthermore, she also exhibited hypocomplementemia, high ESR and increased SLEDAI score.

MAS is a secondary form of acquired Hemophagocytic Lymphohistiocytosis (HLH) in the setting of autoimmune diseases.[2,3] Clinically, it presents with a sudden onset of intense inflammation marked by persistent fever, enlargement of the liver and spleen, liver impairment, swollen lymph nodes, encephalopathy, purpura, and bleeding. In more severe cases, MAS can progress to a life-threatening state of multi-organ failure. This involves dysfunction of the central nervous system, impaired kidney function, respiratory distress, as well as various cardiovascular complications including low blood pressure and shock.[3]

Table VIII. Probability of hemophagocytic syndrome according to the HScore

HScore	*Probability of hemophagocytic syndrome, %*
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

SOURCE: Fardet, L., Galicier, L., Lambotte, O., Marzac, C., Aumont, C., Chahwan, D., Coppo, P., & Hejblum, G. (2014). Development and Validation of the HScore, a Score for the Diagnosis of Reactive Hemophagocytic Syndrome. Arthritis & Rheumatology, 66(9), 2613–2620. https://doi.org/10.1002/art.38690

The pathophysiology proposed in both HLH and MAS, is the failure to induce apoptosis due to cytotoxic dysfunction leading to prolonged expansion of T cells and macrophages and escalating production of pro-inflammatory cytokines.[7] MAS is most associated in systemic juvenile idiopathic arthritis and adult-onset Still's disease (7.7%).[4,6] The occurrence of MAS in SLE in adults, is relatively uncommon (4.6%).[6] Characteristic clinical features of MAS are high, non-remitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, and hemorrhagic manifestations.

Typical laboratory abnormalities include pancytopenia, increased levels of ferritin, liver enzymes, LDH, triglycerides, D-dimers, and soluble interleukin-2 receptor a (also known as soluble CD25), and decreased fibrinogen levels.[8] There is no agreed diagnostic criteria to date for secondary HLH/HLH, but it should be considered in an unwell, feverish patient in certain at-risk populations. MAS in SLE presents at the onset of the first SLE flare in 46% of patients, in whom hypocomplementemia (56%) and positive anti-DNA antibodies (63%) are common. Fever or pyrexia of unknown origin is the cardinal sign of HLH, and is almost always present in children and adults, with primary/familial or secondary HLH/MAS.

There are also no agreed diagnostic criteria to date for secondary HLH, but it should be considered in an unwell, feverish patient in certain at-risk populations.[5] In our patient, fever was present with low complement level, however, anti-DNA was negative. Ferritin is seen at

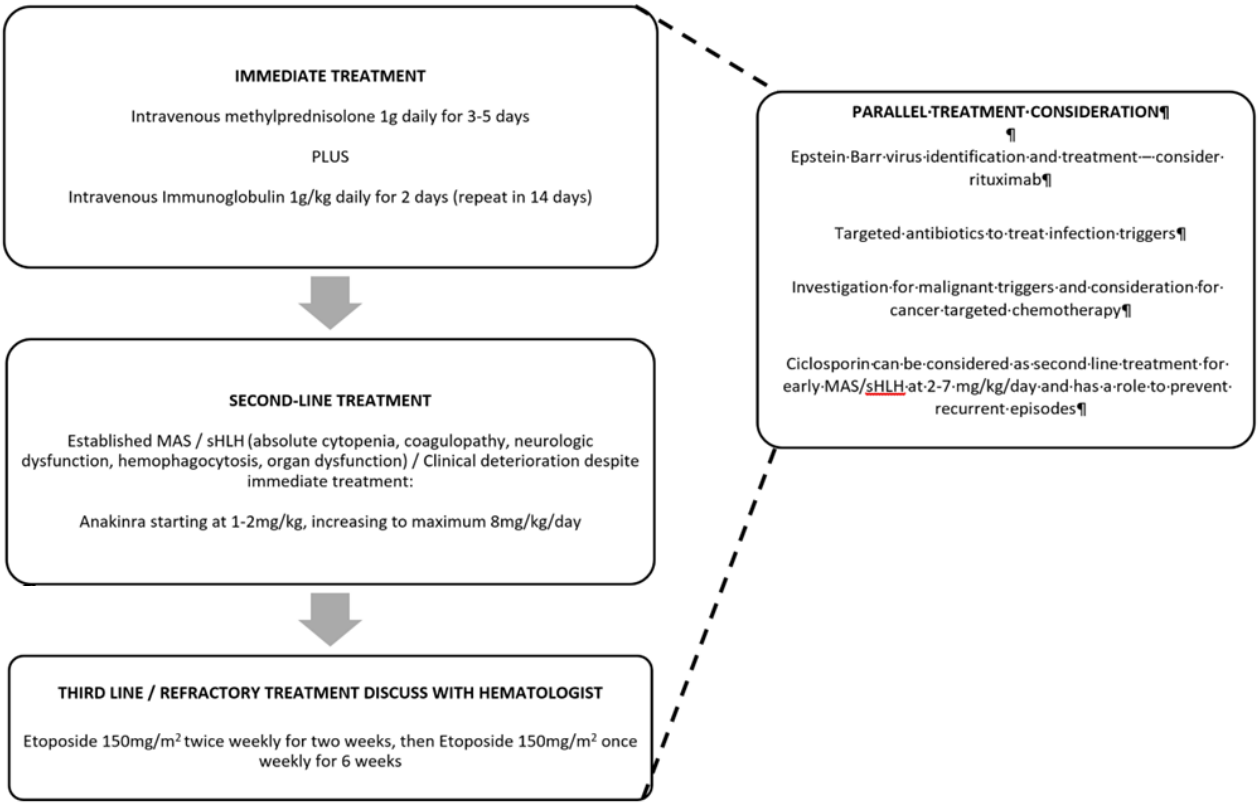

Figure 3. Recommended treatment protocol for adults with MAS/sHLH

Source: Carter, S. J., Tattersall, R. S., & Ramanan, A. V.; Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis, and treatment. Rheumatology, 58(1), 5–17, 2018. https://doi.org/10.1093/rheumatology/key006

extremely high levels in MAS patients and is a distinctive feature. Extreme hyperferritinemia is thought to be secondary to excessive erythrophagocytosis and sequestration of resultant free iron.[17] In the case presented above, ferritin was >1000 µg/L. Based on the algorithm presented by Carter et al, ferritin level between 500-10,000 can be classified as MAS possible. This algorithm suggested to do serial full blood count (FBC), ferritin, fibrinogen, triglycerides, AST, LDH and to perform Hscore.[4]

Patient's initial peripheral blood count upon admission was anemic and thrombocytopenic, but on the third hospital day, repeat count was pancytopenic, a typical finding in HLH. Patient was noted to have elevated triglyceride, AST, and LDH upon admission, also typically seen in HLH. Fibrinogen was not done due to unavailability at our institution. Patient's Hscore was 207, which is said to have a 88% probability of HLH (see *Table VIII*).[16] Fardet et al stated that the best cutoff value for HScore was 169, corresponding to a sensitivity of 93%, a specificity of 86%, and accurate classification of 90% of the patients. However, one limitation is that the cutoff values for the laboratory criteria may depend on the underlying disease.[9] The features of MAS-associated SLE and active SLE are quite similar, so it is difficult to differentiate between these two entities. Lambotte et al reported that 53% of 15 episodes in their MAS-associated SLE patients had cardiac involvement, so one should be aware of MAS in SLE patients if cardiac involvement presents along with other compatible laboratory findings, as in the case-of our patient.[9]

There are no validated treatment protocols for sHLH in adults. Tattersall et al, mentioned that immediate treatment with intravenous methylprednisolone 1g daily for 3-5 days plus intravenous immunoglobulin (IVIG) 1g/kg for 2 days is recommended as first-line treatment. If there are features of established HLH or signs of clinical deterioration despite immediate treatment, anakinra may be used as second-line treatment (see *Figure 3*).[5] A retrospective review by Fukuya et al noted that out of twenty-six cases who fulfilled HPS criteria, high-dose corticosteroid monotherapy was given in 26 cases, being effective in 46%.[6] In our patient, methylprednisone monotherapy was given in which noted significant resolution of clinical and laboratory parameters.

Conclusion

With these findings, we conclude that the diagnosis seen in this case was not explained by SLE alone. A high index of suspicion for MAS should exist in a patient with pyrexia of unknown origin with concomitant autoimmune disease. In this disease that can lead to progressive organ

failure, early diagnosis and management is crucial. This case report culminates the need for diagnostic and therapeutic guidelines that will help in the early diagnosis and immediate treatment of this debilitating condition.

Conflicts of Interest. All authors declare that we have no conflicts of interest regarding the publication of this paper.

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