CLINICAL VIGNETTE

Macrophage Activation Syndrome as Initial Manifestation of Systemic Lupus Erythematosus

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Case Presentation

A 30-year-old female originally from Thailand presented to the Emergency Department for recurrent fever, fatigue and unintentional weight loss for one month. Her fevers were episodic and nocturnal often associated with night sweats. In addition, she reported one week of sore throat, productive cough and rhinorrhea as well as a few days of diffuse rash and loose stools. One month prior to admission, she used amoxicillin for a tooth infection and 1 week prior to admission, she took cetirizine and cephalexin for an upper respiratory tract infection. She has no prior medical history and denies immunodeficiency, malignancy, severe infection, autoimmune or rheumatologic disease. There was no family history of malignancy, blood disease or rheumatologic disease. Upon admission, she was febrile to 38.6 ºC with otherwise stable vital signs. Physical examination revealed facial edema, oral ulceration with erythema along the soft palate, mild alopecia, unilateral posterior cervical lymphadenopathy (0.5 x 0.5 cm), non-pruritic diffuse erythematous facial rash, maculopapular rash involving chest, abdomen, back and lower extremities and right upper quadrant tenderness. Initial laboratory results were notable for pancytopenia with absolute lymphopenia and neutropenia, markedly elevated transaminases of AST 2330 U/L and ALT 1005 U/L, gamma-glutamyl transferase 347 U/L, total bilirubin 2.1 mg/dL, direct bilirubin 1.4 mg/dL, elevated ferritin 15,839 ng/mL, triglyceride 253 mg/dL, lactate dehydrogenase 1214 U/L, d-dimer 9.25 mcg/mL, haptoglobin 22 mg/dL and fibrinogen 207 mg/dL with normal prothrombin time 13.3 sec, INR 1.02, CRP 0.6 mg/dL and ESR 50 mm/hr. Infectious screening including blood, fungal, sputum, stool and urine cultures, hepatitis panel, clostridium difficile toxin, influenza, RSV, respiratory viral panel, mono spot, RPR, HSV 1 and 2, HIV, CMV PCR, EBV PCR, parvovirus B19, coccidioidomycosis serology, (1–3)-β-D glucan assay were all negative. QuantiFERON gold TB was indeterminate but chest X ray was negative for acute process. Immunological screening was significant for ANA (>1:2560, homogenous), anti-dsDNA (1:640), positive anti-phospholipid and low serum component (C3 19 mg/dL, C4 <2.0 mg/dL). Findings for anti-Sm/RNP, anti-histone, anti-mitochondrial, anti-smooth muscle, rheumatoid factor, ANCA, SPEP and UPEP were unremarkable. Urine protein/creatine ratio was 4.3. Coombs test and direct antiglobulin tests were positive and suggestive of autoimmune hemolytic anemia. Further imaging with abdominal ultrasound with doppler studies was negative for thrombus and subsequent abdominal CT examination was only notable for two incidental hepatic hemangiomas. Neck CT examination showed multiple lymph nodes of varying size without neck mass and was otherwise unremarkable. Chest CT examination was unremarkable. Echocardiography showed only mild mitral valve regurgitation. More studies including CK, aldolase, ceruloplasmin were negative. Peripheral smear showed thrombocytopenia, normochromic anemia and multiple acanthocytes without blast cells. Bone marrow biopsy was consistent with occasional hemophagocytosis. Renal biopsy revealed class lV lupus nephritis. No neoplastic process was found in any imaging results, bone marrow and renal biopsy studies. Finally, NK cells activity was decreased to 3 LU30 and soluble CD 25 were elevated to 3986 pg/mL.

With this constellation of clinical presentations and laboratory findings, patient was diagnosed with systemic lupus erythematosus (SLE) according to the ACR/EULAR 2019 classification, given the presence of ANA >1:2560 as well as additive criteria of fever (2pt), leukopenia (3pt), thrombocytopenia (4pt), autoimmune hemolysis (4pt), non-scarring alopecia (2pt), oral ulcers (2pt), acute cutaneous lupus (6pt), proteinuria (4pt), renal biopsy class IV lupus nephritis (10pt), positive lupus anticoagulant and cardiolipin (2pt), low C3 and C4 (4pt) and anti-dsDNA antibody (6pt).[1] Furthermore, in the setting of a confounding underlying rheumatologic disease, the presence of pancytopenia, borderline splenomegaly (11cm), hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, fever ≥38.5°C, hemophagocytosis in bone marrow, decreased NK cell activity, and elevated soluble CD25 fulfilled criteria for a primary diagnosis of macrophage activation syndrome (MAS), a subset of hemophagocytic lymphohistiocytosis (HLH).[2] Overall, these findings led to our final diagnosis of MAS secondary to new onset of SLE.

Patient was initially started on empiric treatment for neutropenic fever with cefepime 2g every 8 hour and vancomycin 1g every 12 hour for a few days. As infectious screening was unrevealing, empiric antibiotic treatment was discontinued and immunosuppressive therapy was immediately started. Initially, our differential diagnosis remained broad including MAS/HLH, SLE, adult onset still's disease, drug induced liver injury and DRESS syndrome. Patient was first started on a trial of 20mg oral prednisone daily, and immediately responded with improved transaminases, total bilirubin, LDH and ferritin with stable haptoglobin, fibrinogen and d-dimer. Given significant

response to steroid, patient was started on IV methylprednisolone 500mg daily for 3 days, then IV methylprednisolone 125mg twice a day for 4 days. As patient continued to improve, we started to taper to dexamethasone 10mg/m^2 daily (15mg po daily) to continue for 2 weeks and at the same time started cyclosporine 3mg/kg daily (75mg po twice a day) for maintenance therapy. Atovaquone 750mg twice a day was started as PCP prophylaxis while on immunosuppressants. Dexamethasone was continued to taper down to 5mg/m^2 for 2 weeks, 2.5mg/m^2 for 2 weeks, then 1.25 mg/m^2 for 2 weeks. Her diffuse malar rash, facial edema, oral ulceration and abdominal pain significantly improved with this treatment. Laboratory findings continued to normalize. Patient was clinically improving and was subsequently discharged to home. On outpatient follow up, patient was also started on mycophenolate mofetil 500mg twice a day, and hydroxychloroquine 200mg daily for further management.

Discussion

HLH is a rapidly progressive fatal syndrome where excessive immune activation could lead to severe tissue damage and ultimately organ failure. HLH can be further defined as primary HLH due to genetic causes or secondary HLH due to infection, rheumatic diseases or malignancy. MAS is an acquired form of HLH that results as a life-threatening complication of rheumatologic disease. It is associated with almost all rheumatic conditions such as systemic juvenile idiopathic arthritis, polyarticular juvenile rheumatoid arthritis, rheumatoid arthritis, sarcoidosis, dermatomyositis, SLE and many others.[3] Precipitating events include flare of underlying rheumatic conditions, viral infections particularly with Epstein-Barr virus, or use of aspirin and other nonsteroidal anti-inflammatory drugs.[4] Macrophages are triggered and abnormally activated due to dysregulation of macrophage-lymphocyte interaction, and this results in cytokine storm leading to hyperinflammatory state.

Both MAS and HLH are a very rare disease of diverse underlying etiologies. The incidence of MAS associated with SLE is reported as 0.9-2.4% and it is far rarer that MAS presents as the initial manifestation of SLE.[5] Clinically, patients present with a constellation of nonspecific symptoms and laboratory findings of underlying disease and MAS/HLH can be similar and subtle. Due to its rarity and ambiguity in initial clinical manifestations, the diagnosis of MAS/HLH can be often missed or significantly delayed. When HLH is left untreated, a median survival is reported to 1.8-2.2 months and even if treated, a median survival remains 54% at 6.2 years.[6,7] With overall poor outcomes of MAS/HLH, the key to improve survival of patients is to maintain a high index of suspicion for MAS/HLH and test for appropriate laboratory markers immediately to achieve early diagnosis and treatment.

The criteria for diagnosis of MAS follows the HLH criteria. Specifically, it requires either to molecularly verify HLH-associated mutations or to meet 5 out of 8 criteria including 1) fever over 38.5°C, 2) splenomegaly, 3) bicytopenias (at least 2 lines including hemoglobin < 9 g/dL, platelets <100 × 10^3/mL and/or neutrophils < 1 × 10^3/mL), 4) hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL), 5) signs of hemophagocytosis in bone marrow spleen, liver or lymph nodes, 6) low or absent NK cell activity, 7) ferritin >500 ng/mL and 8) elevated soluble CD25. To look for a secondary cause of MAS/HLH, extensive infectious, rheumatologic and hematologic evaluation are required. In our patient MAS was triggered by the new onset of SLE. Recently, new diagnostic criteria known as the EULAR guideline has been developed to make a diagnosis of SLE with improved sensitivity and specificity. Including the presence of a positive ANA as an entry criterion, the EULAR guideline uses an additive point system based on 7 clinical domains (constitutional, cutaneous, arthritis, neurologic, serositis, hematologic and renal domain) and 3 immunologic domains (antiphospholipid antibody, complement proteins and highly specific antibodies domains) where a score higher than 10 meets the diagnostic criteria for SLE.

The challenge encountered in this case is to distinguish active SLE from MAS given overlapping symptoms and laboratory findings between the two entities. Generally, MAS can be separated from other underlying etiologies using a ferritin level as a strong indicator for MAS.[8] While the HLH-2004 protocol defines a ferritin level over 500 ng/mL to meet HLH diagnostic criteria, the study shows that a ferritin level over 10,000 ng/mL confirms 90% sensitivity and 96% specificity for HLH.[2,9] The specific tests such as NK cell function and soluble CD25 can be used for further confirmation of MAS/HLH. However, initiation of treatment should be considered without waiting for the results of confirmatory studies if there is a high index of suspicion in order to improve outcomes. Patients with MAS in the context of a rheumatologic disorder, should be treated for underlying cause alone, which may be sufficient as seen in this case. If patients acutely deteriorate or are refractory to the treatment of underlying cause, it is recommended to initiate HLH specific therapy immediately which consists of a series of weekly treatments with dexamethasone and etoposide (VP-16) based on the HLH-94 protocol. If patients do not respond all these therapies, hematopoietic cell transplant needs to be considered. Recently, biologic agents to target specific cytokines including IL-1, IL-6, IL-18 and IFN-γ have been studied and some have shown promising effects.[10] Overall the prime goal for treatment remains to suppress the overproduction of cytokines and control hyperinflammatory state.

In summary, MAS/HLH are an underrecognized life-threatening syndrome caused by abnormal immune activation. The mortality remains high if underdiagnosed or untreated. When clinicians develop a high index of suspicion, it is extremely important to look for an underlying etiology and promptly initiate treatment to achieve for better outcomes. In many patient with MAS, initial treatment includes a trial of high-dose corticosteroids with immunosuppressive therapy. As the clinical course can be aggressive with a rapid progression to organ failure, clinicians can benefit from understanding of diagnostic criteria and treatment for MAS/HLH to attain early diagnosis.

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