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Macrophage Activation Syndrome (MAS) in a Recently Released Prisoner with Systemic Lupus Erythematosus (SLE)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 38
Final Diagnosis: Systemic lupus erythematosus • macrophage activation syndrome
Symptoms: Altered mental status • diarrhea • fever • nausea • vomiting • weight loss
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Rare disease

Background: Systemic lupus erythematosus (SLE) has myriad manifestations that can affect any organ system in the body. Macrophage activation syndrome (MAS) is a disease of uncontrolled lymphocyte and macrophage proliferation and activation, which has various triggers, including autoimmune disorder, viral infection, and malignancy. We report here on MAS as a complication of adult SLE, a rare association in the literature, in a patient with an unknown past medical history.

Case Report: A 38-year-old male patient presented with severe muscle weakness, diffuse abdominal cramps with vomiting and incontinence of stool, confusion, cough, and sweating increasing in severity for about 1 week. He was unable to give a coherent history and according to his family had been released from prison 3 weeks prior, having been in the corrections system for much of his adult life. The diagnosis of new-onset fulminant SLE complicated by MAS was made, noting the profound degree of bone marrow involvement, neuropsychiatric changes, and hyperferritinemia.

Conclusions: Many of the symptoms, signs, and laboratory findings of SLE overlap with those of MAS, and concomitant presence of both of these disease poses unique diagnostic challenges as well as extreme risk to the patient. A robust set of criteria for identifying MAS in the setting of a confounding underlying rheumatological illness does not exist in the adult population; this case illustrates the approach taken by our team to come to this diagnosis.

MeSH Keywords: Leukopenia • Lupus Erythematosus, Systemic • Macrophage Activation

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Background

We report here on a patient with an unknown past medical history, found to have MAS presenting concomitantly with adult SLE, a rare association in the literature. This particularly challenging case, in which there was a significant likelihood of confounding diagnoses, clearly illustrates the diagnostic difficulty of identification of MAS. This condition is likely under-recognized and carries a very high risk of morbidity and mortality. Further work is needed in this area to identify the diagnostic criteria unique to MAS triggered by, or occurring concomitantly with, autoimmune disease such as SLE in adults in a timely manner that can significantly alter the natural disease course.

Case Report

The patient was examined in the Emergency Department of a large community hospital. He was tall and thin, with a height of 188 cm and weight of 78 kg. Cardiopulmonary exam results were unremarkable. Temperature was 39.4°C and vital signs otherwise normal. Most of the neck, upper extremities, and torso were covered with tattoos. He had small ulcers in the mouth, on the lip, and on the palette, as well as shallow ulcerations on the side of the neck. Mucous membranes appeared dehydrated. Hepatosplenomegaly was absent. Inguinal lymphadenopathy was palpable as well as small, non-tender, freely movable axillary and cervical nodes.

He was oriented to his name only but showed appropriate mood and affect. His replies were nonsensical; admitting to having had homosexual relations with multiple partners 30 years prior, as well as claiming to have had 100 000 episodes of diarrhea. He was accompanied by his family members, who reported that the patient may have had schizophrenia or depression diagnosed during his lengthy incarceration, although he was not taking any medications immediately prior to presentation.

Chest X-ray revealed no infiltrates, masses, or cardiomegaly. A CT angiogram of the head was normal for age. Inguinal lymphadenopathy as well as mildly enlarged axillary and cervical nodes were confirmed on CT. The liver, spleen, and pancreas were normal. A peripheral smear did not reveal any blasts, schistocytes, dysmorphic RBCs, or clumped platelets. Urinalysis showed large blood and 6 WBCs, as well as 4 non-dysmorphic RBCs. Protein on dipstick was >300 mg/dl. Serum creatinine kinase was 2283 U/L. Creatinine/BUN was 1.98/39 mg/dL, AST was 155, ALT was 79 U/L, and albumin was 2.8 g/dL. WBC count was 1.83×10^3/µL with a proportionally normal differential, without left shift, platelet (PLT) count was 54/µL, and hemoglobin (HGB) was within normal limits. Urine toxicology was positive for tetrahydrocannabinol only and ethanol was negative.

The patient was treated with intravenous fluid resuscitation, ondansetron, and acetaminophen, and was admitted to the floor with telemetry; his fevers continued, and doxycycline was administered empirically. On the morning after admission, he was able to answer more questions and adamantly denied any medical history but reported losing an estimated 25 pounds over the last few months to a year. He denied intravenous drug use and stated that he had no sexual encounters while incarcerated but reported that extensive tattoo work was done in prison with amateur equipment.

Profound waxing and waning delirium continued, with inattention. Valacyclovir therapy was initiated for possible herpes encephalitis. An extensive infectious workup was undertaken. Blood and urine cultures and gram stains did not reveal any pathogens. Serologic testing for *Anaplasma phagocytophilum*, *Ehrlichia* species, *Cryptococcus*, *Coxiella burnetii*, and a rickettsial panel were negative. QuantiFERON testing for tuberculosis was indeterminate as a result of the low lymphocyte count. A syphilis screen was negative. A full hepatitis battery, HIV, Ebstein-Barr virus, and cytomegalovirus antibody testing were all negative. His diarrhea did not improve in the first week after admission. Stool analysis was negative for cryptosporidium, *Giardia lamblia*, *Clostridium difficile*, IStx-*E. coli*, ova and parasites, and Shiga toxin, and negative for aerobic growth. Fecal fat content was 22%.

Cyclic daily fevers above 38.9°C continued. WBC was now 1.5×10^3/µL and PLT was 50/µL. HGB fell to a low of 11 g/dL, prompting iron studies. Ferritin was markedly elevated at over 6500 ng/mL. LDH was 842 U/L. Iron and TIBC were within normal limits. Sedimentation rate was 24 mm/hr, and CRP was within normal limits. Serum IgA and IgM and IgG were within normal limits. ANA antibody staining returned markedly positive with titers at >1: 320, homogenous pattern; Reflex anti-Sm and anti-dsDNA were both strongly positive. CT-guided bone marrow aspirate and biopsy prep were performed (Figure 1). No erythrophagocytosis was noted, but the sample was partially crushed and there was only a small amount of marrow available for analysis. Iron stores were present and within normal limits. Conclusive bone marrow cell differential could not be analyzed and in the limited sample there were no malignant cells. Cultures for aerobic and anaerobic bacteria, as well as AFB and fungus, were collected.

His mental status continued to deteriorate, and he could not recall members of the health care team coming to see him even 30 min prior. States of complete expressive aphasia would only persist for about 1 h, before a return to a more normal baseline function, albeit with marked confusion. MRI/MRA brain was negative for intracranial abnormalities or vascular disturbances. Haloperidol was initiated. No serositis, synovitis, or joint erythema was appreciated at any point. At this time,

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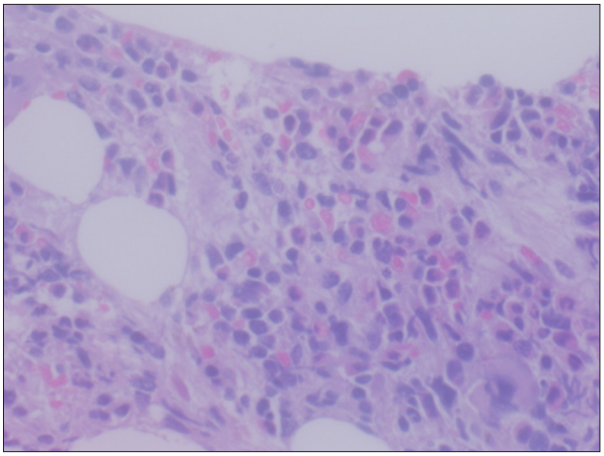

Figure 1. Bone marrow biopsy shows a paucity of myeloid and erythroid precursors, with some focal increases in plasma cells.

hemophagocytic lymphohistiocytosis (HLH) was considered and appropriate laboratory tests were ordered. Triglycerides and d-dimers were elevated at 315 mg/dL and 5.28 µg/L respectively. Fibrinogen levels were 400 mg/dL.

Prednisone 20 mg daily was initiated without improvement in mental status. After three days the dose was increased to 80 mg daily. His fevers resolved 2 days later, with a marked improvement in mental status noted by all interacting health care professionals. Creatinine/BUN decreased to 1.25/26 mg/dL. All microbiology studies, including cultures of bone marrow aspirate, remained negative. The improved CBC prior to discharge showed WBC 2.32×10^3/µL, HGB 11.5 g/dL, and PLT 89/µL. The patient still had burning pain in the toes but was otherwise enjoying a complete resolution of all presenting symptoms. Repeat ferritin did not fall below 5000 ng/mL. He was discharged on steroid taper with instructions to return in 1 week.

He did not return until 20 days after discharge to an outpatient rheumatology office. He had stopped prednisone within a few days of leaving the hospital because of insomnia. A CBC was obtained; WBC was only 0.86×10^3/µL and a differential was unavailable. HGB was 11 g/dL and PLT 96/µL. C3 and C4 complement values were decreased. Sedimentation rate was 44. AST was 369 and ALT was 157 U/L. Albumin was 2.5 g/dL, and creatinine was decreased to 0.96 mg/dL. High-dose prednisone, as well as hydroxychloroquine sulfate and azathioprine, were restarted, and the patient scheduled to return in 2 weeks, but he was lost to follow-up.

Discussion

Our patient presented with a complex and nonspecific constellation of symptoms and abnormalities in several organ systems. Complicating the case was the limited reliability of the patient's history and review of symptoms. Previous medical records were not available, and neither the patient nor his family was sure from which penitentiary he had been released. An infectious etiology was initially suspected in the setting of recent and lengthy incarceration. Lymphadenopathy in the setting of significant fever was also concerning for lymphoma.

Active tuberculosis or pneumonia was unlikely with negative imaging. Neither urinalysis nor blood cultures indicated a source of infection. Acute retroviral syndrome was considered; the combination of mental status changes, mucocutaneous ulcers, leukopenia, and diarrhea was suspicious for HIV/AIDS, and rarely, a self-limited encephalopathy may accompany acute HIV infection associated with seroconversion to HIV. Serum was assayed for HIV1 and 2 with the Ortho VITROS Immunodiagnostic system, which did not provide serological evidence of infection. Due to higher risk in prison populations, an HIV RNA assay was also ordered, and returned negative.

A bacterial and parasitic etiology of disease was largely ruled out. A week after admission, all blood counts worsened, including increasing involvement of the erythrocyte line. Ferritin is an acute-phase reactant that can be markedly elevated in certain autoimmune diseases and malignancy. Autoimmune disorders in the differential included MCTD, polymyositis, and Bechet disease. Hepatocyte injury can also be responsible for high ferritin, and the AST/ALT pattern may have led us to suspect some degree of ethanol ingestion outside of the hospital setting, but no evidence of this was found.

Malignancy or infiltration of the bone marrow was in the differential. A CT-guided biopsy of the iliac crest revealed no evidence of malignant cells but did show an increase in marrow plasma cells. This finding is nonspecific, but may been seen in SLE, often concurrently with an abundance of IgG immunoglobulin. Additional immunological testing revealed that anti-dsDNA and anti-Smith antibodies were markedly elevated, which confirmed the diagnosis of fulminant SLE, but we continued to have suspicions that another process was complicating the clinical picture. Ferritin was elevated well above average levels reported in uncomplicated SLE cases; Indeed, a review of 72 patients with uncontrolled lupus flare found only 2 patients with ferritin levels higher than 5000, with no reported cases over 6000 ng/mL [1].

The cyclic fluctuations in mental function seen in our patient were initially suspected to be malingering, but as the disease progressed, we were convinced that we were seeing a manifestation of an organic process. Neurological involvement is not uncommon in SLE, although symptoms are at times difficult to separate from the adverse effects of high doses of corticosteroids [2]. These symptoms can run the gamut from mildly

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disturbed attention and concentration spans to severe delirium [3]; however, severe delirium appears to be an uncommon neuropsychiatric manifestation of SLE. Profound impairment, as seen in our case, appears to be rare. Higher serum ferritin is associated with CNS involvement and the overall increase in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [4,5]. Our patient's SLEDAI score was elevated, but all of the parameters proposed in the index were not evaluated [1,6].

ESR may be elevated in patients with active SLE, while the CRP is usually in the low normal range in the majority of sufferers. In a febrile lupus patient, marked CRP elevation (greater than 6 or 7 mg/dL) favors the diagnosis of bacterial infection [4,6,7]. We did not have evidence of an infectious process complicating SLE; therefore, we suspected that a hemophagocytic syndrome (HS) could have been responsible for our patient's intense degree of hyperferritinemia, bone marrow suppression, and neuropsychiatric effect.

Viral infections have been known to trigger HS [8,9], including chronic HIV infection. Interestingly, patients infected with HIV comprise a significant fraction of all individuals found to have serum ferritin levels ≥1000 ng/mL [10], but such elevations typically appear to be a marker for relatively advanced disease with low CD4 counts. Several published SLE cases have been reported to be compounded by concomitant HIV infection [11]. Viruses associated with HS that were not assayed include influenza, parvovirus, and coxsackievirus.

Hemophagocytic lymphohistiocytosis (HLH) is a form of HS that is often genetically linked. It is stipulated that 5 of 9 criteria must be met for definitive diagnosis [12], but only 4 of the 9 were seen in our patient. Hepatosplenomegaly was not noted at any point in the clinical course, and NK-cell activity was unfortunately not assayed. Soluble IL-2 receptor levels were elevated at 1800 pg/mL but were not increased by 2 standard deviations above the upper limit of normal, as stipulated in this seminal paper. These diagnostic criteria, however useful, have not been reliable for early MAS, which has historically been considered by many as a form of secondary HLH [13]. An insufficient number of adult SLE cases with concomitant MAS have been studied to develop robust diagnostic criteria specific for this presentation; there are a few similar case reports illustrating HSs that have been triggered by autoimmune disease, including a small number of adult SLE cases.

Criteria for the establishment of MAS in the setting of juvenile systemic lupus erythematosus [14] were met, but it is unclear if these criteria would apply outside of a pediatric cohort: cytopenia, transaminitis, hypertriglyceridemia, and elevated LDH were present in addition to the signs discussed previously. A 2016 article by Ravelli et al. also notes the difficulty in identifying the diagnosis of MAS presenting concomitantly with active juvenile idiopathic arthritis (JIA), identifying the 5 laboratory studies that are most sensitive for identifying MAS [15]. Our patient met all of the stipulated criteria, except for fibrinogen <360 mg/dL.

Recently, an effort was made to quantify the most sensitive criteria for differentiating the manifestation of MAS from multiple underlying autoimmune diseases occurring in children, especially systemic-onset juvenile idiopathic arthritis (SJIA), polyarticular juvenile idiopathic arthritis (PJIA), Kawasaki disease, and juvenile SLE. The diagnosis of MAS was based on clinical and laboratory criteria, and positive bone marrow aspirate findings, if available. According to this analysis, the fall of platelet levels <206 000/microliter or a decrease >30 000/microliter (from baseline values) was the most sensitive indicator to distinguish between MAS and active manifestation of autoimmune disease [13] in the absence of another plausible diagnoses (such as ITP). In this case, the patient presented with low platelet levels, but baseline was not available. The next most sensitive indicator was elevated aminotransferase level. The cut-offs used were AST >38.5U/L and ALT >38U/L. Albumin below 3.0 g/dL was also noted to be a strong predictor, as was ferritin over 5277 ng/mL. All of these criteria were met in our case, further reinforcing the diagnosis of MAS.

Conclusions

Cumulatively, we conclude that the pathology seen in this case was not explained by SLE alone. While demonstration of phagocytosis of erythroid cells by biopsy increases the certainty of the MAS diagnosis, we were not able to obtain this characteristic finding in our limited bone marrow sample. However, bone marrow biopsies often do not show evidence of hemophagocytosis [16], especially in the early stage of MAS. Neither the presence nor absence of such a finding rules MAS in or out [17].

MAS requires a high index of suspicion for identification [18], and it is entirely possible that it is underdiagnosed in fulminant SLE patients, as there are no definitive guidelines for diagnosis [9]. Indeed, MAS has been reported to be the initial presentation of SLE in 26 cases as of 2015 [19–23], mostly in children. It is quite possible that there are more adult patients with SLE and MAS that have responded to early steroid intervention and have not been investigated further.

Initial treatment for this condition therefore remains a trial of high-dose corticosteroids, and it is estimated that 50% of patients will have good response [24]. Cytotoxic therapies may be used as a second-line treatment after immunosuppressant failure; cyclophosphamide is used [18,20,23], especially in cases with prominent renal involvement. Immunomodulators such

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as mycophenolate, hydroxychloroquine sulfate, and anti-metabolites such as azathioprine play a role in treatment of MAS and the underlying rheumatological disorder. Rituximab has also been used to good effect [24]. Reports have been made of MAS patients non-responsive to best current medical therapy, who have had resolution after splenectomy [16,17].

Close follow-up is important, as the risk of relapse is high in MAS patients, especially if immunosuppressants are prematurely discontinued, as has been illustrated in this case. The clinical course for patients can be aggressive, with a quick progression to renal failure, shock, sepsis, and death [1,20]. Attempts have been made to quantify diagnostic criteria in the pediatric population, as discussed, but a robust set of guidelines is needed to identify this extremely serious and likely under-recognized disease, especially in the adult hospitalized population.

Conflict of interests

None.

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