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Adult-onset still's disease with macrophage-activation syndrome presentation in a critically ill woman in the second trimester of pregnancy: A case report

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Abstract

Background: A rare inflammatory illness known as Adult-Onset Still's Disease (AOSD) is typically characterized by a high fever, arthralgias, and a transient rash of salmon hue. Systemic immune hyperactivation syndrome known as Hemophagocytic Lymphohistiocytosis (HLH) can occur as a primary process in those with a genetic predisposition or it can be brought on by another disease, frequently a viral infection or cancer. When a rheumatologic condition serves as the trigger, secondary HLH is referred to as Macrophage Activation Syndrome (MAS). Reduced natural killer (NK) cell activity, increased soluble interleukin-2 receptor (sIL-2R), and generally, excessive cytokine production appear to be components of both AOSD and MAS pathogenesis.

Case description: We present a case of a 36-year-old female G3P2 who presented with suspected sepsis due to pyelonephritis, with initial labs showing significantly elevated liver function tests including aspartate transaminase (AST) 2,710 U/L and alanine transaminase (ALT) 711 U/L, as well as ferritin over 100K. After extensive testing to exclude infectious and autoimmune causes the Yamaguchi criteria for AOSD were fulfilled, and a diagnosis of AOSD complicated by MAS was made. Her condition improved with steroid therapy.

Conclusions: We show a unique presentation of AOSD in the first trimester of pregnancy, complicated by MAS. Due to a multidisciplinary approach and empiric corticosteroid treatment, there was a favorable outcome. We hope that other emergency room and critical care medical professionals will consider this rare diagnosis in complex pregnant patients with transaminitis.

Keywords: Adult onset stills disease (AOSD); Macrophage activating syndrome (MAS); Pregnancy; Transaminitis; Hemophagocytic lymphohystiocytosis (HLH).

Abbreviations: AOSD: Adult-Onset Still's Disease; MAS: Macrophage Activating Syndrome; HLH: Hemophagocytic Lymphohistiocytosis; AST: Aspartate transaminase; ALT: Alanine transaminase; MFM: Maternal Fetal Medicine.

Introduction

Here we report a case of a young pregnant women presenting in her second trimester with Adult Onset Still's Disease (AOSD) complicated by Macrophage Activation Syndrome (MAS). AOSD is a systemic autoinflammatory process which classically manifests as fevers, arthralgias, pink maculopapular rash, along with lymphadenopathy and hepatosplenomegaly [1]. Giacomelli's et al. comprehensive systematic literature review placed the prevalence at 0.16-0.4/100,000 [2]. First line treatment is glucocorticoids and nonsteroidal anti-inflammatory drugs, and most cases present in patients with prior autoimmune conditions. MAS as the presenting symptom in AOSD is a rare phenomenon, especially in pregnancy. With the complexities of a pregnant patient with AOSD with MAS, there are no clear guidelines in place on how to best come to the diagnosis or treat the condition. This case report hopes to add to our clinical exposure to the literature in order to raise awareness of the potential diagnosis and help aid in the multidisciplinary treatment plan to improve prognosis.

Case Presentation

A previously healthy 36-year-old woman G3P2, 16 weeks into her third pregnancy, presented to an affiliated institution's emergency department with fever and lab abnormalities necessitating transfer to our institution where she was admitted to the ICU for sepsis. Pertinent past medical history included a history of migraines for which she was taking Tylenol every 4 to 6 hours, as well as a recent UTI treated with Nitrofurantoin. No other pertinent medical or family history was obtained. She was empirically treated with vancomycin and piperacillin-tazobactam and supported with high flow nasal cannula for acute hypoxic respiratory failure. Her initial laboratory investigation revealed significant transaminitis including aspartate transaminase (AST) 2,710 U/L and alanine transaminase (ALT) 711 U/L. NAC protocol was initiated pending results of further workup. Pertinent additional significant laboratory findings early in the admission included a rising leukocyte count 13.3/uL, hemoglobin 8.6 g/dL, and platelets 224/uL. Haptoglobin of less than 10 mg/dL. The rest of the liver function tests were abnormal as well, increasing alkaline phosphatase and total bilirubin both elevated to 225 U/L and 2.9 mg/dL respectfully, and albumin was decreased to 2.7 g/dL. Ferritin was extremely elevated at >100,000 ng/mL, and LDH peaked early at 3,945 U/L. Triglycerides were elevated at 584 mg/dL. CRP was 23.2 mg/dL and fibrinogen was 504 mg/dL. D-Dimer was elevated at 4.00 ug/mL.

Given multiple lab derangements, a broad differential diagnosis was considered with all treatments being monitored by the maternal fetal medicine (MFM) department. Doxycycline was added to the antibiotic regimen given the possibility of an atypical pneumonia. Also, empiric corticosteroid treatment was initiated cover autoimmune conditions. Despite exhaustive testing, both the infectious (Table 1) and hematological (Table 2) workup were grossly negative. A bone marrow biopsy and aspiration were pending

evaluation, as was soluble IL-2 serum concentration. On imaging, a right posterior liver hemangioma was spotted with no other abnormal findings. On echocardiography a mildly reduced ejection fraction (45%) was seen with hypokinesis of the inferior myocardial wall and a mild pleural effusion. Bilateral lower lobe consolidations were documented via chest X-ray. By day 8 of the hospitalization the patient's laboratory findings significantly improved and the patient was dispositioned out of the ICU to MFM's ward. A clinical diagnosis of AOSD was made via the Yamaguchi criteria. Soluble IL-2 came back increased 2,783 U/mL, more than two times the normal reference range (137-838 U/mL). The bone marrow biopsy came back positive for potential HLH/MAS. The marrow was described as 30-50% hypocellular with rare histiocytes containing red blood cells and small lymphocytes. The final diagnosis of AOSD complicated by MAS was made and the patient was discharged to be followed as an outpatient on hospitalization day 13.

Discussion

AOSD is a rare rheumatic disease which has a systemic effect on the body. Between 0.16 and 0.4/100,000 persons are thought to be its approximate incidence, and both men and women are often affected equally. It primarily occurs in a bimodal distribution between the ages of 15 to 25 and 36 to 46 [2]. Frequently occurring fevers, an ephemeral rash, and arthralgias are just a few of the many systemic symptoms that Still's illness exhibits. It is not uncommon for pharyngitis to be the presenting symptom, with lymphadenopathy, serositis, and hepatomegaly as examples of other concurrent symptoms [3]. Classic symptoms of the illness include quotidian fevers and salmon-colored rashes that frequently appear simultaneously. However, it should be emphasized that several cutaneous symptoms, such as urticaria, widespread pruritus, plaques, and pustules, have been linked to AOSD [4]. AOSD is a clinical diagnosis often made with the Yamaguchi criteria, however excluding other causes is also often needed. Clinicians must first rule out other rheumatologic, infectious, and malignant conditions as well as medication reactions before confirming the diagnoses.

Given the presentation, a wide differential was cast covering infectious, oncological, rheumatological, and medication induced causes. Drug induced liver disease was an initial thought due to the history of migraines with Tylenol use, and recent completion of a nitrofurantoin course. As well, at the influx of negative results from the infectious panel, a unique TB presentation was considered due to a positive quantiferon test. This was ruled out quickly with sputum PCR. Malignancies, specifically lymphoma, were considered, which was one of the reasons a bone marrow biopsy was elected to be done.

After an extensive workup turned up negative, and while the HLH/MAS panel and bone marrow biopsy results pended, the diagnosis via exclusion of an atypical AOSD seemed plausible. The Yamaguchi criteria consist of four major criteria: fever, arthralgia, typical rash, leukocytosis, and five minor criteria: sore throat, lymphadenopathy or splenomegaly, liver dysfunction, and the absence of rheumatoid factor (RF) and antinuclear antibody (ANA) [5]. To make the diagnosis, five criteria need to be met, with two of them being major criteria. In our case, the two major criteria were fever and leukocytosis, and the three minor criteria were splenomegaly, liver dysfunction shown as elevated LFT's, and negative RF and negative ANA. Furthermore, all other causes for transaminitis were ruled out.

Table 1: Negative infectious studies preformed.

Negative Infectious Tests		
Hepatitis B Serologies	Blood cultures (bacterial and fungal)	Q Fever
Hepatitis D Serologies	Urine cultures	R. Typhi IgG and IgM
Hepatitis C Serologies	Nasal methicillin-resistant staphylococcus aureus PCR	Entamoeba histolytica IgG
EBV virus serologies and PCR	Urine legionella antigen and sputum culture	Ehrlichia chaffeensis Serologies
CMV virus serologies and PCR	Syphilis immunoassay	Anaplasma phagocytophilum DNA
HIV antibody and antigen screen	Urine strep pneumoniae antigen	Trypanosoma cruzi
Herpes simplex virus 1 and 2 PCR (positive IgG serologies)	Lyme disease antibody	Strongyloides serologies
HHV6 PCR	Rocky mountain spotted fever	Coccidioides antibody
Parvovirus serologies	Tuberculosis sputum PCR	Aspergillus
Adenovirus PCR	MTB Complex	Fungitell 1 ⟶ 3B-D-Glucan Assay

Complete panel of all infectious causes which were tested for in this patient which returned negative results. Polymerase chain reaction (PCR).

Table 2: Negative rheumatologic studies preformed.

Negative Rheumatologic Tests		
Normal Immune Profile: IgG, IgA, IgM, C3, C4	Anti-Centromere antibodies	Rheumatoid factor antibodies
Coombs Test	Anti-ds DNA antibodies	Anti-ribonucleoprotein (RNP) antibodies
Nuclear Antibody Screen	Anti-Jo-1 antibodies	Anti-SSA/Ro and Anti-SSB/La antibodies
Antinuclear Antibody (ANA)	Anti-mitochondrial antibodies	Anti-Topoisomerase (SCL-70) Antibodies
Antineutrophilic cytoplasmic antibody (ANCA): Myeloperoxidase (MPO) Antibodies and Proteinase 3 (Pro 3) Antibodies		

Comprehensive autoimmune panel which was tested for in this patient which returned negative results. Serum values for immune profile were as follows [IgG (1170), IgA (272), IgM (1197), C3 (97), C4 (37)].

MAS is one of the most dreaded hematologic problems linked to AOSD and may affect up to 10-15% of persons with the condition [6]. A cytokine storm, coagulopathy, and hemophagocytosis are the results of an unchecked and dysregulated immune response that characterizes MAS, a highly inflammatory illness [6,7]. Mortality rates for MAS in rheumatologic diseases can range from 30 to 40 percent [8]. It has been linked to various rheumatologic conditions such as systemic juvenile idiopathic arthritis and systemic lupus erythematosus (SLE). In addition to hematological malignancies and some solid tumors, MAS has also been noted with viral, bacterial, fungal, and parasitic infections [9]. It is very rare for AOSD to have an initial presentation in pregnancy, and it is even rarer for MAS to be the presenting symptom.

Regarding the management of our patient, we think the most important component to her positive prognosis was the early intervention with a multidisciplinary team. This allowed us to quickly stabilize the patient's condition and rule out many of the potential life-threatening causes within a few days. Additionally, it was the different approaches and ideas that allowed us to hone in on the diagnosis of AOSD com-

plicated by MAS quickly and start steroid treatment within the first few days of hospitalization. There were discussions between doctors in infectious disease, rheumatology and MFM about the risks of high dose steroid treatment and the empiric antibiotic treatment the patient was on. There was a strong consensus that the benefits of treatment outweighed the risks of the medications chosen and administered.

Conclusion

In conclusion, we show that MAS can be the presenting complaint of AOSD even in pregnancy. It can mimic peripartum illnesses such as acute fatty liver of pregnancy, preeclampsia or HELLP syndrome depending on the week of presentation. The typical articular and dermatologic symptoms of AOSD may not manifest and pulmonary and cardiac involvement are also possible. The importance of a multidisciplinary approach, especially in the case of pregnancy, cannot be understated. Clinicians should take this uncommon diagnosis into account when assessing a pregnant patient with unexplained fever and multiorgan failure.

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Data availability statement: All data generated or analyzed during this study are included in this article.

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