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Case Report

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A Diagnostic Dilemma: Adult-Onset Still's Disease With Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome?

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Abstract

Adult-onset Still's disease (AOSD) is a rare autoinflammatory condition. It is a diagnosis of exclusion by ruling out all related infectious, inflammatory, autoimmune, and malignant diseases. We present a case of a 23-year-old Caucasian male who presented with fever, night sweats, joint pain, weight loss, and diarrhea. The initial presentation delayed the diagnosis. Upon further investigation, we formulated the diagnosis of AOSD. In sporadic cases, AOSD with secondary hemophagocytic lymphohistiocytosis (HLH), also known as macrophage activation syndrome (MAS), is a devastating disorder of uncontrolled immune activation characterized by clinical and laboratory evidence of extreme inflammation. In case of suspected secondary complications, timely involvement of a multidisciplinary team and starting of appropriate medications is necessary.

Keywords: Adult-onset Still's disease; Hemophagocytic lymphohistiocytosis; Macrophage activation syndrome; Steroids; Inflammatory

Introduction

In evidence-based medicine, correctly diagnosing a disease can sometimes be challenging. We need substantial laboratory and pathological evidence in addition to a clinical picture to formulate a diagnosis. One such case intrigued us to come up with a final diagnosis. A 23-year-old Caucasian male presented to the hospital with fever, night sweats, joint soreness, weight loss, generalized body aches, and diarrhea. We concluded that the patient has adult-onset Still's disease (AOSD) with presumed hemophagocytic lymphohistiocytosis (HLH), also known as macrophage activation syndrome (MAS) upon extensive workup. AOSD is a systemic inflammatory disorder characterized by prolonged spiking fever, evanescent salmon-colored rashes, polyarthralgia or arthritis, leukocytosis, and other manifestations involving multiple organs. AOSD is rare and generally has a good prognosis, but it can also predispose patients to HLH/MAS. Furthermore, secondary HLH/MAS is rare but life-threatening [1-5]. Therefore, timely interventions are necessary for this scenario where HLH is suspected in patients with AOSD to avoid mortality and morbidity.

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Case Report

Investigations

A 23-year-old Caucasian male presented with fever, night sweats, generalized body aches for 2 weeks. Besides that, the patient had 20 lb of unintentional weight loss, three to four watery bowel movements per day, and bilateral ankle and knee joint soreness. A few days before the presentation, he developed a self-resolving, intermittent facial rash spreading to his arms and back. The patient was monogamous and had no recent travel history. He lives in a house in the Midwest part of the USA. Upon presentation in the emergency room, the patient was diaphoretic, tachycardiac, and noted a temperature of 39.5 °C. No rash, joint swelling/tenderness, or lymphadenopathy was noticed on initial examination. The patient's family history was unremarkable, except his paternal uncle died of an unknown blood disorder.

His initial workup was positive for stool *Clostridium difficile* antigen. The rest of the workup, including complete blood count, complete metabolic panel, blood smears, blood cultures, thyroid-stimulating hormone, stool studies, chest X-ray, computed tomography (CT) of brain, abdomen, and chest, was negative for any acute findings (Table 1). Transthoracic ultrasound of the heart was negative for any infective endocarditis. The patient was empirically started on ceftriaxone, doxycycline, and oral vancomycin. The additional workup for common bacterial and viral infections, including antinuclear antibody (ANA), rheumatoid factor (RF), sedimentation rate (ESR), and C-reactive protein (CRP), was sent (Table 1, 2). His fever and diarrhea resolved 3 to 4 days after admission. The patient started to complain of shortness of

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Table 1. Patient's Laboratory Results From Day One to Seven Weeks Follow-Up

Analyte	Day 1	Day 2	Day 3	Day 4	Day 9	Day 10	Day 11	Two weeks later	Five weeks later	Seven weeks later	Reference values
Hemoglobin (g/dL)	12.3	9.9	10.2	10.2	8.0	7.8	8.2	11.5	11.4	11.6	14 - 17
WBCs count (/µL)	10.7	8.4	8.7	7.7	21.3	19.5	19.5	16.3	6.0	6.1	400 - 10,000
AST (U/L)	66	75	164	304	216	181	895	251	94	34	0 - 35
ALT (U/L)	75	78	167	491	481	518	683	172	86	89	0 - 35
ALP (U/L)	84	94	123	141	273	267	243	211	168	73	36 - 92
CRP (mg/dL)		13.8			17.3	33.2	58.2	3.0	0.7	13.2	0 - 0.8
hsCRP					432.3			> 10.0			
ESR (mm/h)		29			56	50	87	20	10	16	0 - 15
D-dimer			1,520								
Ferritin (ng/mL)		376			1,289	1,863	14,549	1,593	331	98	15 - 200
Fibrinogen (mg/dL)						140					150 - 350
Triglycerides (mg/dL)					86						≤ 150

WBCs: white blood cells; AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; CRP: C-reactive protein; hsCRP: high-sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate.

breath and required 2 L of oxygen to maintain oxygen saturation. CT pulmonary angiography (CTPA) was negative for pulmonary embolism (PE). During the hospital course, the patient developed transaminitis (Table 1). Ultrasound of the right upper quadrant showed mild hepatomegaly. Hepatobiliary iminodiacetic acid (HIDA) scan was normal. We initially thought that transaminitis was related to doxycycline-induced cholestasis/hepatitis. Doxycycline was discontinued. The patient was maintaining oxygen saturation on room air. A decision was made to discharge home and follow up in the outpatient clinic in 1 week.

The patient complained of worsening generalized body aches, anorexia, and weight loss during the follow-up visit as he lost an additional 15 lb. The patient also complained of bilateral ankle joint soreness. In addition, the patient was complaining of scant evanescent erythematic rashes spread all over the body after discharge from the hospital. Again, we ordered additional workup. Workup was significant for leukocytosis and transaminitis with significantly elevated CRP, ESR, ferritin, and white blood cell counts. Hemoglobin was also noted to be decreased from previous results (mentioned as day 9 in Table 1). The patient was hospitalized again for further workup and treatment. During the second hospitalization, patient was again started spiking fever up to 39.2 °C.

Diagnosis

We excluded main pathological processes like viral or bacterial infections, malignancy, autoimmune conditions (Table 2). Bacterial, protozoal, and viral infection workup included tuberculosis, malaria, *Babesia*, *Isospora*, *Cyclospora*, *Giardia*, *Salmonella*, typhoid, Lyme disease, leptospirosis, *Ehrlichia*, chlamydia, gonorrhea, syphilis, rotavirus, *Yersinia*, *Campylobacter*, human immune deficiency virus, hepatitis A, B and C, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, coxsackie, measles, mumps, rubella, and parvovirus. Autoimmune workup was also negative to this point (Table 2). Differentials at this stage included AOSD, AOSD with secondary HLH/MAS, infection, or occult malignancy that is not evident in the labs and imaging. The final diagnosis was imperative to start the treatment as the patient's condition was deteriorating. As the patient met the criteria for AOSD as per Yamaguchi criteria for diagnosis of AOSD [2], diagnosis of having AOSD was formulated. Nevertheless, at the same time, the patient was meeting four out of eight criteria for diagnosis of MAS as per 2004 MAS criteria [3] and 2016 MAS classification criteria [4].

Treatment

The patient was started on high-dose steroids. His inflammatory markers are trending down slowly, and liver function tests (LFTs) are still trending up, but the patient was clinically doing slightly better. Therefore, a decision was made to discharge him on oral prednisone follow-up with a rheumatologist was scheduled. During the follow-up visit, the patient did relatively well on steroids and was started on sarilumab, an interleukin-6 (IL-6) inhibitor in addition to steroids.

Follow-up and outcomes

During follow-up, we stopped prednisone, and the patient was started on methotrexate in addition to sarilumab. On follow-up visits, patient's laboratory results were relatively normalized, and the patient was doing clinically well.

Discussion

AOSD is a systemic inflammatory disorder of unknown etiology. The typical presentation involves a high-grade fever

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Table 2. Autoimmune Workup Result

Analyte	Result	Reference value
Antinuclear antibody	Negative	
Rheumatoid factor	Negative	
pANCA	Negative	
cANCA	Negative	
Anti-CCP	Negative	
IL-2 receptor α (CD25), soluble Il2 Recep SerPl-mCnc	2,473	532 - 1,891 pg/mL
Mitochondrial M2 antibody (IgG)	Negative	
LKM-1 antibody (IgG)	Negative	
Actin (smooth muscle) antibody IgG	Negative	
SCL-70 antibody	Negative	
Centromere antibody	< 1.0	AI < 1.0
Cardiolipin IgG	< 1.6	0.0 - 19.9 GPL U/mL
Cardiolipin IgM	0.6	0.0 - 19.9 MPL U/mL
Tryptase	1.8	< 11.0 µg/L
HLA B27	Negative	
Deamidated gliadin antibody, IgA	Negative	
tTG antibody, IgA	Negative	

pANCA: perinuclear antineutrophil cytoplasmic antibodies; cANCA: cytoplasmic antineutrophil cytoplasmic antibodies; CCP: cyclic citrullinated peptides; IL: interleukin; IgG: immunoglobulin G; LKM: liver kidney microsomal; SCL: scleroderma; IgM: immunoglobulin M; HLA: human leukocyte antigen; IgA: immunoglobulin A; tTG: tissue transglutaminase; AI: antibody index.

(> 39 °C), evanescent rash, arthritis or arthralgia, hyperferritinemia, and multiorgan involvement [5, 6]. AOSD is rare, so diagnosis can sometimes be challenging. AOSD is a bimodal disease, usually found between ages 15 - 25 and 36 - 46 years. AOSD incidence ranges between 0.16 and 0.4/100,000 people, and the estimated prevalence rate is 1 - 34 cases per million people and is equally distributed between both genders [5]. Pathogenesis of AOSD is complex and least studied compared to other rheumatological conditions. More recent evidence suggests that both autoinflammatory and autoimmune pathways are involved. Excess activation of IL-1, IL-6, IL-8, IL-18, interferon-gamma (IFNγ), and tumor necrosis factor-alpha (TNF-α) have been studied in the pathogenesis of AOSD [5-7]. AOSD is an acquired disease, but specific individuals have also studied recent familial genes and immune susceptibility. Both viral and bacterial infections are suggested as possible triggers for AOSD. AOSD is a diagnosis of exclusion by ruling out all other infectious, malignant, and autoimmune pathologies [6]. ANA and RF are usually negative in AOSD patients, but they can present in less than 10% of patients [7].

Different diagnostic criteria have been proposed for AOSD diagnosis based on the combination of clinical and laboratory findings. Yamaguchi's criteria are the most sensitive (93.5%), followed by Cush's (80.6%) and Calabro's (80.6%) to detect AOSD [5]. Yamaguchi criteria are divided into major and minor criteria [2]. Major criteria are: 1) fever of 39 °C or higher (≥ 1 week); 2) arthralgia (≥ 2 weeks); 3) salmon-colored maculopapular rash; 4) leukocytosis (≥ 10,000/µL with ≥ 80% granulocytes). Minor criteria are: 1) sore throat; 2) lymphadenopathy and splenomegaly; 3) liver dysfunction; 4) negative RF and ANA tests.

Five features of Yamaguchi criteria, including at least two primary criteria, must be present for AOSD diagnosis. Our patient had four major features of Yamaguchi criteria: fever, arthralgia, leukocytosis, and rash. In addition, the patient also met two features of Yamaguchi minor criteria: liver dysfunction and negative RF and ANA.

There is a paucity of universally accepted nomenclature and diagnostic criteria for diagnosing secondary HLH and MAS in the presence of AOSD. These two conditions overlap in the majority of criteria mentioned in the literature. When HLH occurs in the context of rheumatological diseases, such as systemic juvenile idiopathic arthritis (sJIA), AOSD, or systemic lupus erythematosus (SLE), it is often referred to as MAS [8]. Both conditions are often discussed as one group of diseases under the umbrella of "histiocyte disorders" [8]. For clarity, we will consider secondary HLH and MAS as the same disease class in this article.

HLH is a rare, life-threatening immunological syndrome characterized by the uncontrolled activation of cytotoxic lymphocytes and macrophages, resulting in cytokine-mediated tissue injury and multiorgan dysfunction [8]. HLH can be familial (FHLH) or secondary. Secondary HLH is driven primarily by acquired factors, such as chronic inflammation, infection, or malignancy. Therefore, early recognition and prompt treatment of HLH/MAS are critical for patient survival. Typical laboratory abnormalities include pancytopenia, increased lev-

Table 3. Diagnostic Guidelines for HLH

1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥ 2 lineages
a. Hemoglobin < 9 g/dL
b. Platelets < 100×10^9/L
c. Neutrophils < 1.0×10^9/L
4. Hypertriglyceridemia and/or hypofibrinogenemia
a. Triglycerides ≥ 265 mg/dL
b. Fibrinogen ≤ 150 mg/dL
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK cell activity
7. Ferritin ≥ 500 µg/L
8. sCD25 (i.e., sIL-2R) ≥ 2,400 U/mL

HLH: hemophagocytic lymphohistiocytosis; NK: natural killer; sIL-2R: soluble interleukin 2 receptor.

els of ferritin, liver enzymes, lactate dehydrogenase, triglycerides, D-dimers, and soluble IL-2 receptor α (also known as soluble CD25 (sCD25)), and decreased fibrinogen levels [4]. HLH diagnostic criteria (i.e., HLH 94 and HLH 2004) were developed to recognize children with FHLH for inclusion in clinical trials. For the lack of better tools, clinicians have relied on these criteria for diagnosing other forms of HLH. According to the updated HLH 2004 criteria, diagnosis of FHLH requires five of the eight features (Table 3) [9].

In secondary forms of HLH, identifying and addressing disease triggers (infection, drugs, and malignancy) is a critical therapy component. Usually, these conditions are treated with high-dose intravenous (IV) corticosteroids, targeted IL-1 blockade, or cyclosporine A [8]. Unfortunately, despite significant advances in the last two decades, mortality in HLH remains unacceptably high, especially in adult forms of the disease.

In our patient, a timely secondary HLH/MAS diagnosis was essential to avoid morbidity and mortality. At the same time, with such a diagnosis, it is essential to involve a multidisciplinary team that can treat patients in emergency circumstances where initial interventions are not getting favorable outcomes. Diagnosis of AOSD was reached based on Yamaguchi criteria. The patient was also meeting four out of eight criteria for diagnosis of secondary HLH/MAS. Due to vague nomenclature and classification, it is hard to decide the exact diagnosis in specific clinical scenarios. Our treatment team thought we needed more laboratory data to go with a secondary HLH/MAS diagnosis. To obtain more histopathological and molecular evidence was a time-consuming process. Treatment targets are different if we consider secondary HLH/MAS in AOSD. There is still confusion in the literature on when to consider specific treatments in case complications arise from AOSD. The early use of steroids is a widely accepted treatment in the literature. TNF-α inhibitors (etanercept, adalimumab, and infliximab), IL-6 receptor inhibitors (tocilizumab and sarilumab), and IL-1 Inhibitor (anakinra, canakinumab) have demonstrated efficacy both as monotherapy and in combination with disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of acute to chronic inflammatory immune-mediated diseases including AOSD. These drugs selectively inhibit the pathways involved in disease pathogenesis, as mentioned above [10-15]. Fortunately, our treatment plan worked in favor of the patient, and the patient became clinically stable. Subsequent use of sarilumab and methotrexate also kept the disease in remission at a 6-month follow-up.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from the patient in written.

Author Contributions

OP contributed to idea conception, data gathering, and writing. ASA contributed to proofreading.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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