Successful Management of AOSD with Deflazacort: A Case Report

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Abstract

Adult-Onset Still's Disease (AOSD) is a rare multi-systemic inflammatory disorder with an undetermined etiology. This condition is characterized by a broad spectrum of symptoms that may include a daily spiking fever, salmon colored maculopapular rash and arthritis. Commonly mistaken for viral infections or other rheumatological disorders, this is a disease of exclusion and usually follows a long-convoluted path to diagnosis. We present a case of a 42-year-old Georgian woman with spiking fevers, a maculopapular rash affecting her hands and neck, arthritis and ankle swelling. After treatment with a series of drugs, our patient was found to satisfy the Yamaguchi criteria and was successfully treated with a combination of Deflazacort and Methotrexate. Our study established that a diagnosis of AOSD is strongly suggested by presence of pyrexia of unknown origin and certain specific clinical findings. We saw a favorable outcome in our patient after the initiation of Deflazacort and Methotrexate.

Keywords: AOSD, deflazacort, Still's disease, maculopapular rash, autoimmune, arthritis

Introduction

Adult-onset Still's Disease (AOSD) is a rare systemic autoinflammatory disease of unestablished etiology and pathogenesis, categorized by a high intermittent fever, inflammatory polyarthritis and salmon-colored maculopapular rash. In 1896 George Still, described a form of juvenile idiopathic arthritis. In 1971, Eric Bywaters coined the term AOSD to describe adults presenting with similar symptoms.[1,2] The clinical presentation includes non-specific symptoms and histopathological findings; thus diagnosis requires exclusion of other diseases. Life-threatening complications may include Macrophage Activation Syndrome (MAS), Disseminated Intravascular Coagulation (DIC), cardiac tamponade and respiratory distress syndrome.[4]

Case Report

A 42-year-old Georgian woman presented with lower back pain and ankle swelling for the past 2 weeks. She had no fever, myalgia, rash, morning stiffness, ocular symptoms or oral ulcers. She has a history of neurosis, depression and no significant prior hospitalizations. Normal vital signs except for hypertension and elevated pulse rate. Physical examination was unremarkable except for physical findings of anemia.

Hematological test results are tabulated as Test Results-1 [Table 1]. She was prescribed iron supplements and 400 mg of Ibuprofen which was ineffective. X-rays showed scoliosis, subchondral vertebral sclerosis with osteophytes, and sacroiliitis with sclerotic articular surfaces and narrowed joint spaces. Doppler ultrasonography showed venous insufficiency of the saphenous vein and branches. Anti-nuclear Antibody (ANA) titers were positive (1:160). She was then diagnosed with reactive arthritis and prescribed 8 mg of oral methylprednisone daily, providing marginal pain

relief. Despite treatment compliance for 6 months, she developed a non-pruritic salmon colored maculopapular rash on her neck, upper chest and hands and fever with a double quotidian pattern that fluctuated throughout the day with spikes of 38.5°C (101.3°F). This occurred in 2021 during the COVID-19 pandemic, so the patient dismissed her symptoms as being COVID-19-related despite multiple negative Sars-Cov-2 PCR results.

Table 1: Hematological test results.

Hematological test	Test result	Test result 2	Normal Range
Hemoglobin	8.7 g/dL	10.3 g/dL	12-16 g/dL
Red Blood Cell	3.84 million/µL	4.02 million/µL	4.2-5.4 million/µL
White Blood Cell	5.3 thousand/µL	12.02 thousand/µL	5-10 thousand/µL
Platelet count	373,000/µL	432,000/µL	130,000 – 360,000/µL
C- Reactive Protein	22 mg/L	-	0-6 mg/L

Due to side effects, the patient refused to continue methylprednisone. Dermatologist and allergologist evaluation collectively ruled out any primary dermatologic or allergic disease origin. She was then prescribed Seysara (5 mg daily) and Ketotifen (1 mg daily) for 10 days, with no symptom improvement.

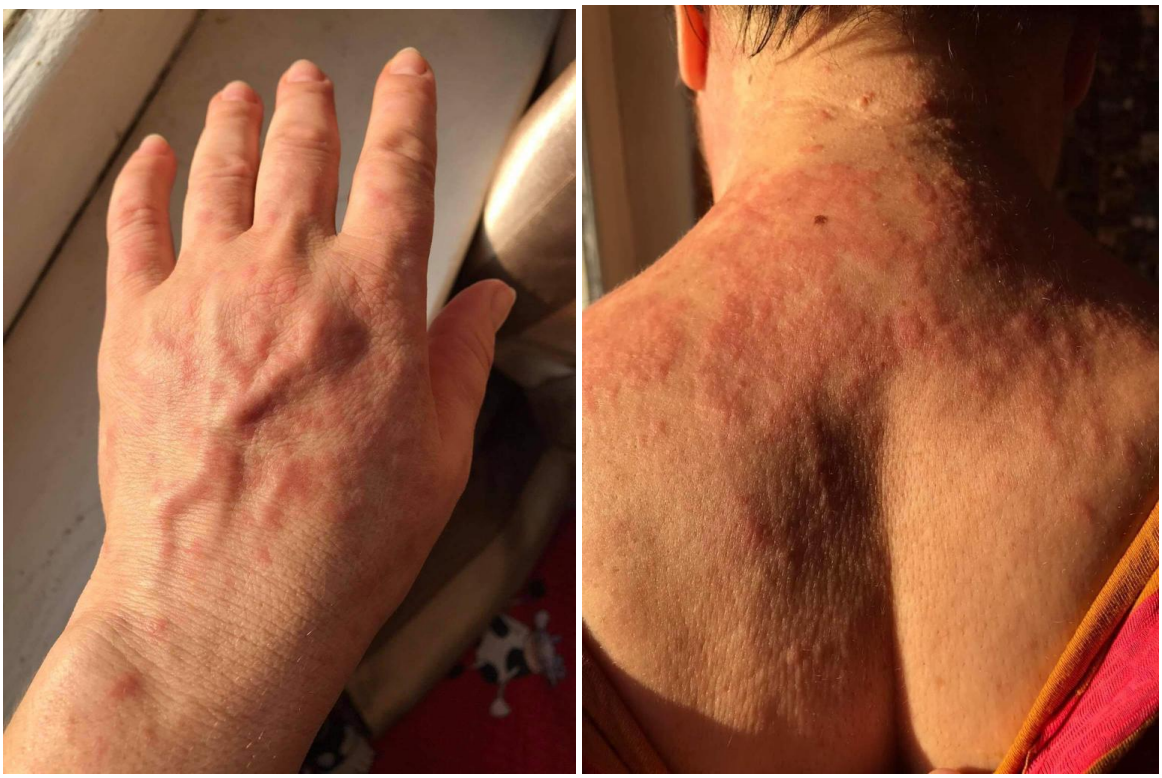

Figure 1: Characteristic salmon pink maculopapular rash as seen on our patient.

Repeated Hematological test results are tabulated as Test Results 2 (Table 1) and Immunological tests were performed (Table 2).

Based on clinical findings, the patient was diagnosed with AOSD, presenting with all 4 major findings of the Yamaguchi criteria. Deflazacort was started (6 mg twice daily) for 1 week. Her condition improved greatly with the rash remaining in clusters dorsally on the hands and normalized temperature.

Consequently, therapy with Deflazacort (24 mg/d, 6mg x 4 tablets and Methotrexate (2.5 g per week) was initiated, significantly improving symptoms. Deflazacort was tapered, reducing 3 mg every 2 weeks and is currently on 10.5 mg.

Table 2: Immunological test result.

Immunologic test	Test result	Normal Range
Antinuclear Antibody	1:160, mitotic (centrosome/centriole)	1:<80
Anti-cyclic Citrullinated Peptide	21.1 EU/ml	N<20 EU/ml
C3	normal	
C4	normal	
Anti-double Stranded DNA (Anti-dsDNA)	negative	
Antineutrophilic cytoplasmic antibody	negative	
Anti-La antibodies	negative	
Anti-Ro antibodies	negative	
Anti-Hepatitis B antibodies	negative	
Anti-Hepatitis C antibodies	negative	
Anti-Human immunodeficiency virus (HIV) antibodies	negative	
anti-SARS-Cov immunoglobulin	negative	
Anti-cardiolipin antibodies	negative	

Discussion

AOSD is a chronic, systemic inflammatory disease marked by quotidian fever, inflammatory arthritis, elevated WBC count and evanescent rash. It is rare with an incidence of 0.1-0.4 cases per 100,000 people in Europe, no gender preference, and a bimodal age of onset (15-25 and 36-46 years).[2] Although its cause is unknown, it's believed to be a reactive syndrome with genetic factors and infectious agents like Yersinia enterocolitica and Mycoplasma pneumoniae being implicated.[5] This may be as Toll like receptors (TLRs) play a significant role in the host's defense against microorganisms,[6] initiating, and maintaining the inflammatory response in AOSD. Additionally TLRs influences the clinical characteristics in AOSD.[7]

Two immune pathways drive AOSD: innate immunity activation of neutrophils and macrophages via pro-inflammatory cytokine IL-18 and elevated levels of various cytokines (IL-1, IL-6, IL-10 TNF-α, IFN-γ, TGF-β1) play a central role in the disease, making them potential therapeutic targets.[5] Transforming growth factor beta (TGF-β1)[8] and interleukin-10 (IL-10) are pivotal in maintaining immune homeostasis and exhibiting an anti-tumor effect.[9] IL-10 has dual effects on stimulating natural killer (NK) cells and inhibiting monocytes, a feature which may significantly contribute to the pathogenesis of AOSD,[10] making them potential therapeutic targets.[5]

Diagnosing AOSD is challenging, often being mistaken for infectious or autoimmune conditions, due to the common presentation of arthralgia and rash, delaying diagnosis by 1.5-4 years.[11] Other common symptoms are pharyngitis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, pericarditis, pleurisy, and abdominal pain. Fever is sudden onset, often ≥ 39°C, follows a daily pattern, spikes in the afternoon and generally precedes other symptoms. Fever can spontaneously resolve[12] or in about 20% of cases show incomplete defervescence, where it persists between spikes or experiences an additional spike in the morning.[2] The rash (seen in 75-95% of patients) is typically transient, salmon-colored appearance, maculopapular, non-pruritic and emerges alongside the fever. Predominantly occurring on the trunk and extremities, it can also manifest on the palms, soles, and face. Arthritis can initially manifest as mild, short-lived, and oligoarticular, but has the potential to progress to being symmetric and polyarticular, causing significant joint damage.[2] Commonly impacted joints include the knees, wrists, and ankles. However, elbows, hips, shoulders, phalangeal and temporomandibular joints can also be affected. Myalgia typically exacerbates during fever spikes.[2]

Elevated levels of inflammatory markers, specifically Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), are observed in most patients.[2] Other hematological observations include leukocytosis, often surpassing 15,000 cells/microL, with neutrophilic predominance > 80%, along with normocytic normochromic anemia, and thrombocytosis. Approximately 70% of individuals have remarkable increases in serum ferritin levels, and is associated disease activity.[13] The Red Cell Distribution Width (RDW) serves as a readily available inflammatory biomarker.[14] Additionally, it proves to be a swift and valuable tool in distinguishing between Adult-Onset Still's Disease (AOSD) and sepsis during the early stages. An RDW value equal to or greater than 14.8% indicates a higher likelihood of sepsis compared to AOSD in patients initially presenting with fever and requiring hospitalization.[15] On the other hand, the Mean Platelet Volume (MPV) provides information about the average platelet size, measured in femtoliters, serving as an indicator of the variability in platelet size.[16] This metric could be utilized as a supplementary biomarker for the differential diagnosis of AOSD and sepsis. Notably, the MPVs in the AOSD group were significantly lower than those observed in sepsis cases.[17]

Macrophage activating syndrome, a life-threatening complication of AOSD presents similarly to an AOSD flare-ups with hepatosplenomegaly, fever and increased ferritin. It may lead to end organ damage and death and is often associated with leukopenia, thrombocytopenia, hypertriglyceridemia and elevated lactate dehydrogenase.[18]

Currently, the diagnosis of AOSD is based on classification criteria, due to the lack of specific clinical manifestation or biomarkers. Several sets of classification criteria have been proposed for AOSD. The most commonly used are Yamaguchi (Table 3) and Fautrel classification (Table 4).

Table 3: Yamaguchi criteria Exclusion Criteria: Infection, Malignancy, Other Rheumatic diseases.[19]

Major Criteria	Minor Criteria
Fever of 39 °C or more for at least 1 week	Sore throat
Arthritis or arthralgia for 2 or more weeks	Lymphadenopathy
Non-pruritic salmon colored rash	Hepatomegaly or Splenomegaly
Leukocytosis with 10,000/µl or greater with granulocytes (80%)	Abnormal liver function tests
	Negative tests for Rheumatoid Factor (RF) and Anti-Nuclear Antibody (ANA)

Yamaguchi criteria has a sensitivity and specificity of 96% and 98%, respectively.[18] To meet these criteria, patients must fulfill five criteria, including at least two major criteria.[19] Fautrel criteria has a sensitivity and specificity of 80.6% and 98.5% respectively. To meet the criteria for diagnosing AOSD, the patient must have three or four major and at least two minor criteria.[20]

The neutrophil to lymphocyte ratio (NLR) is a marker of inflammation that indicates the level of systemic inflammation in the body.[21] Research has shown that elevated NLR levels are associated with poor prognosis in various conditions including major cardiac events, ischemic stroke, and cancer. In classifications such as Fautrel and Yamaguchi, a neutrophil percentage of 80% or higher is considered a significant criterion. The NLR (≥ 4) has the potential to serve as a sensitive biomarker for diagnosing adult-onset still's disease (AOSD), potentially replacing the neutrophil percentage ($\geq 80\%$) in the classification criteria (Yamaguchi and Fautrel classification).[22]

Table 4: Fautrel criteria, Exclusion Criteria: Infection, Malignancy, Other Rheumatic diseases[20]

Major Criteria	Minor Criteria
Spiking fever of 39 °C or more	Maculopapular rash
Arthralgia	Leukocytes $\geq 10{,}000/mm^3$
Transient erythema	
Pharyngitis	
Polymorphonuclear count $\geq 80\%$	
Glycosylated ferritin $\leq 20\%$	

Treatment goals include minimizing inflammatory damage and preventing complications. Main treatment options include NSAIDs and corticosteroids. Prednisone is started at doses of 0.5-1 mg/kg/day until symptom control, after

which it is tapered. For unresponsive and severe presentations, Disease-modifying anti rheumatic drugs (DMARDs) like Methotrexate and Cyclosporine A and biological treatments like Anakinra (IL-1 antagonist), Canakinumab (Anti-IL-1β monoclonal antibody), Tocalizumab (IL-6 antagonist) and Infliximab (TNF-α antagonist) are used. Patients requiring high doses of steroids and DMARDs have a high relapse tendency following steroids tapering. In patients with MAS, DIC and other severe complications, intravenous pulse steroid therapy is indicated.[13]

Conclusion

AOSD, a rare systemic inflammatory disease is a challenging diagnosis due to the absence of specific serological markers and should be a potential diagnosis when dealing with fever of unknown origin. Exclusion of AOSD should not rely on serum ANA and low ferritin as it may atypically present, as in our case. Prompt diagnosis and treatment provide a favorable outcome. Delayed diagnosis of our patient was due to physicians attributing her symptoms to the general COVID-19 symptoms afflicting people during the pandemic.

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