An Unusual Cause of Fever, Rash, and Joint Pain: A Case Report of Adult Onset Still's Disease

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ABSTRACT

Background: Adult-Onset Still's Disease is a rare inflammatory disorder with an estimated incidence of 1 in 1,000,000 that presents with a rash, fever, and arthritis. Furthermore, there have only been three reported cases in the Philippines. Its presentation is similar to other more commonly encountered inflammatory disorders; however, it is the negative immunologic and serologic workup that typically distinguishes this rare specific inflammatory disorder along with the fulfillment of diagnostic criteria set by Yamaguchi and Cush.

Case: This is a case of an 18-year-old female who presented with recurrent fever, rash, and polyarthritis. The patient underwent extensive workup, but immunologic studies were negative. A consideration of Adult-Onset Stills Disease was made and along with the fulfillment of the classification criteria set by Yamaguchi and Cush, the diagnosis was clinched and the patient was started on glucocorticoid therapy where improvement of the patient's condition was noted with the resolution of the fever, rash and minimal complaints of joint pain.

Conclusion: Adult-Onset Still's Disease is an uncommon inflammatory disorder that confers high morbidity and disability. It commonly presents with shared clinical features among other inflammatory disorders; thus, recognition of the existence of this disease entity could pose a diagnostic dilemma. A high clinical suspicion along with negative studies and fulfillment of the diagnostic criteria avoids unnecessary workup and inappropriate management.

Keywords: *Still's Disease, Arthritis, Autoimmune, Yamaguchi Criteria, Cush Criteria, Fautrel Criteria*

INTRODUCTION

Adult-Onset Still's Disease (AOSD) is a rare inflammatory disorder with a characteristic manifestation of daily recurring fever, arthritis, and rash. It is an uncommon disease with an incidence of 1 in 1,000,000 people with 0.16 new cases per 100,000 people with no predilection between males and females. In the Philippines, there are only 3 reported cases in the Philippines since 2015.[1] A bimodal age of distribution is noted.[2]

This report presents a case of an 18-year-old patient diagnosed with AOSD, a disease whose etiology and pathophysiology are not fully elucidated, thus leading to its under-diagnosis. Should the disease continue to be so, will lead to significant morbidity and disability.

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CASE PRESENTATION

This is a case of an 18-year-old Filipino female student who had no known co-morbidities and was admitted for the first time in this institution due to the recurring problem of fever and multiple joint pain and swelling.

There was an unremarkable family history, with no history of rheumatologic disorders such as Systemic Lupus Erythematosus or Rheumatoid Arthritis, in the family.

The patient had onset of arthralgia 9 months before admission, which was first noted in both knees with a pain scale of 5 out of 10. The arthralgia progressed to arthritis, spreading from the knees to both ankles, eventually affecting both wrists, and was now noted to be debilitating with a pain scale of 10 out of 10. This was associated with intermittent fever with the highest recorded temperature of 39.6° Celsius. Interventions done to alleviate the condition include the intake of Paracetamol 500 mg/tablet 1 tablet taken as needed for the pain, providing only temporary relief.

In the interim, there were repeated attacks of arthritis and fever, however, no consult was done with the patient tolerating the condition and taking Paracetamol as needed for pain and fever.

One week before admission, there was a recurrence of fever and arthritis, now associated with the onset of a generalized nonpruritic erythematous maculopapular

Table 1. Complete Blood Count

Parameter	Result	Reference
White Blood Cells	25.8	4-10
Neutrophils	89.3	47-80
Lymphocytes	6.8	13-40
Monocytes	3.1	2-11
Eosinophils	0.1	0-5
Basophils	0.6	0-2
Red Blood Cells	3.3	4.5-5.9
Hemoglobin	8.69	13.5-17.5
Hematocrit	26.6	41-53
Mean Corpuscular Volume	79.1	80-100
Mean Corpuscular Hemoglobin	25.9	26-34
Mean Corpuscular Hemoglobin Concentration	32.7	31-36
Platelets	500	140-440

Table 2. Immunology-Serology Laboratory Results

Parameter	Result	Reference
High Sensitivity C-Reactive Protein (HSCRP)	114.65	0-5
Erythrocyte Sedimentation Rate (ESR)	75	0-20 in Female 0-10 in Child
C3 Complement	164	-
Coomb's Test Direct Indirect	 Negative Negative	 - -
Procalcitonin	0.28	< 0.05
Anti-Nuclear Antibody (ANA)	Negative	< 40
Rheumatoid Factor (RF)	2	< 15
Anti-Citrulinated Cyclic Protein (Anti-CCP)	11	< 20
Ferritin	945	7-140

rash that started at the chest and spread throughout the patient's body noted to occur with the onset of fever and disappear during afebrile periods. This prompted the family to seek consult at Cebu City where the patient sought consult with a specialist and was subsequently advised admission for further work-up and management.

On admission, the patient was febrile and non-ambulatory with complaints of inflamed and tender joints and dysphagia and was at first managed as a case of Infectious Arthritis and started on Ciprofloxacin 500 mg/tablet 1 tablet taken twice a day. Pertinent physical examination findings include the presence of a generalized nonpruritic erythematous maculopapular rash at the chest and both upper and lower extremities, erythematous pharynx with the absence of inflammation and exudates of both tonsils, absence of lymphadenopathy, especially in the cervical region, absence of tenderness, hepatomegaly, splenomegaly on abdominal examination, and presence of tenderness and partial limitation in the range of motion of both knee joints, both wrist joints, and both ankle joints. A complete blood count (CBC) was taken and revealed leukocytosis with neutrophilic predominance (*Table 1*). However, procalcitonin levels were inconclusive with a possible local bacterial infection and unlikely systemic bacterial infection. Two sets of blood cultures from

Table 3a. Yamaguchi Criteria

YAMAGUCHI CRITERIA			
Major Criteria		**Minor Criteria**	
Fever of more than 39 degrees for more than 1 week	Yes	Sore Throat	Yes
Arthralgia or arthritis for more than 2 weeks	Yes	Lymphadenopathy	No
Typical rash	Yes	Increased LFT	Yes
WBC of more than 10,000 with 80% PMN	Yes	RF and ANA negative	Yes
Presence of 5 or more criteria, with at least 2 being major – YES Sensitivity: 96% Specificity: 92%			

Table 3b. Cush Criteria

CUSH CRITERIA			
Major Criteria		**Minor Criteria**	
Fever of greater than 39 degrees	Yes	WBC count greater than 15,000	Yes
Arthralgia or arthritis	Yes	Typical rash	Yes
Rheumatoid factor less than 1:80	Yes	Pleuritis or pericarditis	No
ANA less than 1:100	Yes	Hepatomegaly, splenomegaly or lymphadenopathy	No
Major criteria require all criteria to be met – YES **Minor criteria require 2 of the criteria to be met** - YES Sensitivity: 85% Specificity: 97%			

Table 3c. Fautrel Criteria

FAUTREL CRITERIA			
Major Criteria		**Minor Criteria**	
Fever of greater than 39 degrees	Yes	Maculopapular rash	Yes
Arthralgia	Yes	Leukocytosis greater than 10,000/mm^3	Yes
Transient erythematous rash	Yes		
Polymorphonuclear cells greater than 80%	Yes		
Glycosylated ferritin less than 20%	No		
Diagnosis requires the following conditions to be met: **Four major criteria** – YES OR **Three major criteria and 2 minor criteria** - YES Sensitivity: 80.6% Specificity: 98.5%			

peripheral sites were taken but revealed no growth of any organism. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were taken which were all elevated (*Table 2*). An ultrasound (UTZ) of the abdomen was taken revealing the absence of spleen enlargement and otherwise normal results. A consideration of Systemic Lupus Erythematosus (SLE) was made, however work-up for SLE was unremarkable with negative anti-nuclear antibodies (ANA) and only fulfilling 2 points of the 2015

ACR Revised Criteria for Diagnosis of Systemic Lupus Erythematosus; meaning that this was only a possible case of SLE. The patient was then referred to a Rheumatologist for further work-up and management. Rheumatoid Arthritis was considered and subsequently ruled out with negative rheumatoid factor (RF) and anti-cyclic citrullinated protein antibodies (Anti-CCP).

The health care team reached a diagnostic dilemma, with all immunologic work-up being negative (*Table 2*). A diagnosis of AOSD was considered, thus the three major diagnostic criteria for AOSD were taken into account. The Yamaguchi criteria require 5 or more criteria to be fulfilled; with 2 being major to be fulfilled to make a diagnosis of AOSD; with the patient meeting all 4 major criteria and 3 minor criteria. The Cush criteria require all major criteria and 2 minor criteria to be met; with the patient meeting all 4 major criteria and 2 minor criteria. Serum ferritin was taken and was noted to be increased, which was taken as a serologic marker and to monitor response to treatment. The Fautrel criteria require 4 or more major criteria or 3 major and 2 minor criteria to be met; with the patient meeting 4 major criteria and 2 minor criteria (*Tables 3a–c)*.

The goal of therapy was to control the patient's symptoms while minimizing adverse effects, thus a plan to start systemic steroids was made. The patient was started on Prednisone 20 mg/tablet 1 tablet after breakfast and 10 mg/tablet 1 tablet after dinner with a total daily dose of 30 mg. Gradual but remarkable improvement in the patient's arthritis, with a pain scale of 1-2 out of 10 and minimal limitation in the range of motion of the joints affected, and resolution of fever and rash was noted.

The patient was then discharged with improved condition with minimal complaints of joint pains and no recurrence of febrile episodes. The plan was to continue systemic corticosteroids with Prednisone for 2 weeks with gradual tapering thereafter. Close follow-up was done every 2 weeks for 2 months and then monthly thereafter for a year. On the first follow-up, a repeat CBC, ESR, CRP, and Ferritin were to be taken to monitor the patient's condition. Adverse events were to be expected, mostly due to the side effects of systemic steroid use such as hyperglycemia, weight gain, decrease in bone density, increased risk for infection, and increased risk for peptic ulcers. If on the first follow-up, there is no noted improvement in the patient's condition, a plan for starting Methotrexate at a dose of 7.5 mg once a week was contemplated. The prognosis of the patient's condition in terms of functionality is good, with early initiation of therapy and the absence of shoulder and hip involvement; which are markers of an unfavorable outcome.

DISCUSSION

Adult-Onset Still's Disease is a rare inflammatory disorder characterized by recurring daily fever, arthritis, and rash.[1] Its incidence is noted to be rare with only 1 in 1,000,000 people or 0.16 new cases per 100,000 people, with no gender or racial predilection. In the Philippines, there have only been 3 reported cases since 2015. A bimodal age of distribution is noted with one peak between the ages of 15 to 25 and the second peak between the ages 35 to 45, with the patient belonging in the first peak of incidence.[2]

This course of this inflammatory disease follows three main patterns: a monophasic pattern, with a course that lasts weeks to months and resolves within a year. An intermittent pattern, with multiple intermittent disease flares with periods of remission in between lasting years. A chronic pattern that presents with persistently active disease.[3] A pattern could not be elucidated in the patient's case, as this was the first occurrence of symptoms.

The clinical features of the disease include fever, joint pain, and rash, occurring in 75 to 95% of patients. In the patient's case, all characteristic features of the disease were present. The fever is usually characterized as occurring daily and usually precedes the other symptoms. AOSD should be considered in some cases of Fever of Unknown Origin (FUO).[4] The rash of AOSD is usually characterized as macular or maculopapular, nonpruritic and tends to occur with febrile episodes and dissipates during remission of fever. It predominantly involves the trunk and extremities. Koebner's phenomenon may be present, with eruptions elicited by stroking the skin or found in areas of pressure applied by clothing. Arthralgia and arthritis are the most consistent feature of AOSD. Initially mild and affecting a few joints, the disease evolves into a more severe and possibly destructive polyarthritis. A characteristic feature of AOSD but present only in a few patients is the fusion of the wrist joints.[5] Other clinical manifestations that may be present in AOSD include pharyngitis; manifesting as severe, nonsuppurative pharyngitis, hepatomegaly, pericarditis, pleural effusion, lymphadenopathy; usually in the cervical region, and splenomegaly. The disease pattern of patients with AOSD can be divided into 3 distinct types.[6]

A. Monocyclic or Self-limiting pattern – single episodes of systemic disease of variable duration followed by complete remission

B. Polycyclic or Intermittent pattern – two or more episodes of systemic disease separated by a symptom-free remission period lasting for a minimum of 2 months

C. Chronic articular pattern – severe articular manifestations causing joint destruction

An elevation in acute phase reactants is seen in AOSD, which includes: ESR, CRP, and serum ferritin, which were all appreciated in the patient and are seen in at least 70% of cases. The elevations in serum ferritin correlate with disease activity and are suggestive as a serologic marker to monitor the response to treatment.[7] The acute phase response is typically accompanied by hematologic abnormalities that include leukocytosis that exceeds 15,000 cells/μL with a predominance of granulocytes, normocytic, normochromic anemia with hemoglobin less than 10 g/dL in a majority of patients, as was seen in the patient's CBC picture. Elevated liver enzymes and lactate dehydrogenases are seen in 75% of patients. Antinuclear antibodies and rheumatoid factor are present in only 10%

of patients and are typically low in titer. In the patient's case, ANA, RF, and Anti-CCP were all negative. Synovial fluid analysis is usually inflammatory in picture with WBC averaging at 13,000 cells/µL but can range from 100 to 48,000 cells/µL. Other findings include a slight proliferation of the cells in the synovial lining layers, moderate vascular engorgement, and a mononuclear cell infiltrate.[8] It must be taken into account, however, that laboratory examination findings for AOSD are characteristic but non-specific as they are seen in other inflammatory disorders as well.

The differential diagnoses that may be considered are diverse and generally categorized into 3: infectious, rheumatologic, and malignancy. Infectious considerations include viral syndromes such as hepatitis; however, the patterns of fever in viral infections differ from the typical daily fever pattern of AOSD. Systemic bacterial infections also present with fever, leukocytosis, and elevated acute phase reactants; however, systemic bacterial infections usually present with positive blood cultures. Rheumatologic considerations include systemic rheumatic diseases including SLE and RA, as they present with arthritis and elevated acute phase reactants. Considerations of malignancy include Lymphoma, especially Non-Hodgkin's and Hodgkin's Lymphoma as they present with fever, lymphadenopathy, and leukocytosis. Systemic Lupus Erythematosus was a primary differential diagnosis entertained in this case. But due to a negative serologic work-up and only a possible case of SLE by using the 2015 ACR Revised Criteria for the Diagnosis of Systemic Lupus Erythematosus, SLE was unlikely.

There is limited data on the diagnosis and treatment of AOSD, with most data confined to medical literature such as case reports, small series, and retrospective studies. Thus, making a diagnosis of AOSD is difficult and is often made clinically, which requires the exclusion of infectious, neoplastic, and other autoimmune diseases. There are no characteristic serological biomarkers available, with laboratory tests being not specific and only reflective of heightened immunologic activity.[9] Thus, a detailed history and thorough physical examination with selected laboratories are needed and utilized to arrive at a diagnosis of AOSD. Several diagnostic criteria have been proposed and among them, Yamaguchi's, Cush's, and Fautrel's criteria being the most employed.[10] Among the three, the Yamaguchi criteria is most widely used due to the criteria having the highest sensitivity and specificity among the rest. All these criteria are a helpful guide in making a diagnosis of AOSD. All three criteria, however, lack the combined sensitivity and specificity to be useful for clinical diagnosis and rely heavily on the exclusion of other conditions.[11] In the patient's case, the extensive diagnostic work-up, which ruled out other inflammatory disorders and fulfillment of the Yamaguchi, Cush, and Fautrel criteria, clinched the diagnosis of AOSD. This approach was similar to the diagnostic approaches used in published case reports on AOSD, where only after extensive workup was done and potential differential diagnoses were ruled out, was a diagnosis of AOSD based on the different diagnostic criteria available.[6,11]

The goals of therapy in AOSD include controlling physical signs and symptoms of inflammation, preventing end-organ damage, and minimizing the risk of adverse effects of therapy including long-term effects of glucocorticoid use such as hyperglycemia, reduced bone density, and increased risk for peptic ulcer disease and infection.[12]

The therapy in AOSD in approached by classifying patients according to their disease severity:

A. Mild - presents with fever, rash, and mild arthritis, and responds to nonsteroidal anti-inflammatory drugs alone, but may require low dose glucocorticoid therapy

B. Moderate - presents with high fever, debilitating joint symptoms, and signs of organ involvement that are not life-threatening, these require glucocorticoid to control the inflammatory response and disease manifestations

C. Severe - presents with life-threatening organ involvement such as cardiac tamponade and disseminated intravascular coagulation, with patients requiring high-dose or pulse glucocorticoid therapy and should receive early intervention with a biologic agent such as interleukin 1 or 6 inhibitors.

Glucocorticoid therapy is initiated with Prednisone at a dose of 0.5 to 1 mg/kg/day; as was done in the management of the patient where Prednisone 20 mg/tablet 1 tablet in the morning and Prednisone 10 mg/tablet 1 tablet in the evening with a total cumulative dose of 30 mg daily. Evaluation of response to therapy is done after 2 months on glucocorticoids. In patients who do not respond to glucocorticoids are then approached based on their more predominant symptoms.[13,14] In patients with an arthritis predominant disease, glucocorticoids are shifted to Methotrexate 7.5 to 15 mg given once a week.[15, 16] In patients with rash and fever as the predominant symptom, Anakinra 100 mg is given daily subcutaneously. For those who do not respond to Anakinra, Tocilizumab is given and Canakinumab is given for those who cannot tolerate the daily injections of Anakinra. In patients who do not respond or achieve disease control on Methotrexate after 3 months of therapy with 2 months on maximal dosing of Methotrexate at 25 mg weekly, a tumor necrosis factor inhibitor is generally added, such as Infliximab.[17,18] In the patient's case, with the case classified as moderate in severity, therapy was initiated with Prednisone and with a plan for the inclusion of Methotrexate to the therapeutic regimen if the condition does not respond to the initial agent started.

The prognosis of AOSD in terms of functionality is good, even if with a chronic disease pattern but depends on the type of involvement and if treatment is initiated early. Development of an erosive polyarthritis during the initial disease episode and involvement of the shoulder and hips are generally associated with an unfavorable outcome.[19]

CONCLUSION

Adult-Onset Still's Disease is a rare occurrence, with only 1 in 1,000,000 people affected and to this day, remains a diagnostic dilemma. Due to its inflammatory nature, a combination of nonspecific symptoms, and lack of specific serologic markers, it remains a diagnosis of exclusion with diagnosis mainly made clinically. Despite the rarity of this disease entity, it should be considered in patients who present with symptoms of fever, rash, and arthritis. It must be emphasized that a detailed history and physical examination together with a focused diagnostic work-up with a high index of suspicion be made to avoid a delay in the diagnosis, initiate timely and appropriate management to improve outcomes and limit disability.

Informed Consent

Informed consent was obtained after a thorough explanation of the patient's condition, the rarity of the said condition, and the contribution it could make in the advancement in understanding AOSD by making a case report on the patient's condition.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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