Adult-Onset Still's Disease: A Rare Cause of Pyrexia of Unknown Origin (Case Report with Literature Review)

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Abstract

Adult-onset Still's disease (AOSD) is a remarkably rare illness. One well-known pathogenic process that results in systemic manifestations is auto-inflammatory disease. We report on a young man who complained of joint pain, sore throat, and a high spiking fever. After a thorough assessment using the Yamaguchi criteria, the patient's clinical examination, elevated serum ferritin and C-reactive protein (CRP), absence of serologic markers (RA factor, Antinuclear antibody levels), and lymphadenopathy all contributed to the diagnosis of AOSD. He was treated with analgesics, steroids, and disease-modifying anti-rheumatic drugs (DMARDs). Three weeks later, at the follow-up, his symptoms and lab parameters had improved.

Keywords: *AOSD, hyperferritinemia, DMARDs, PUO, arthralgia.*

INTRODUCTION

AOSD is an uncommon, auto-inflammatory systemic condition that primarily affects women [1].

Clinical signs include neutrophilic leucocytosis, elevated serum ferritin titers, joint pain, brief salmon-colored skin rashes, and a high spiking fever. In addition to these general features, AOSD patients may also have neurological signs, sore throat, and cardiac and kidney problems [2]. It is one of the few unusual reasons for pyrexia of uncertain etiology [3]. The diagnosis cannot be supported by any particular biomarkers. Since AOSD is an exclusionary diagnosis, the patient must undergo extensive testing to rule out other differential diagnoses, such as infections, cancer, and other rheumatic diseases, that have similar clinical symptoms [4].

CASE PRESENTATION

A 25-year-old factory worker who was normotensive, non-diabetic, non-addicted, and intellectually slow first showed up with joint pain two months ago and a high spiking fever two weeks later along with throat discomfort. According to the patient, his joint pain started in his wrist and knees before moving on to other joints. He experienced joint stiffness for around 30 minutes in the morning, and the discomfort was so bad that he was unable to do his regular tasks. He had a high fever of 102 °F, which was only momentarily reduced by antipyretics. He denied having ever experienced any rash on his body, red eyes, cough, loose stools, abdominal pain, alopecia, mouth ulcers, or photosensitivity. He previously had pulmonary tuberculosis eight years ago, for which he received six months of therapy.

On examination, a young man with average- build and height, well oriented, with vitals of Temperature: 102°F, Bp: 130/70, Pulse: 94 bpm, Respiratory rate: 17/minute, Spo2: 97% at room air. He had anemia and showed no signs of dehydration, cyanosis, clubbing, leukonychia, or koilonychia. His cervical lymph nodes were palpable, movable, not adhering to the skin above them, and there was no discharge from lymph nodes.

The shoulder and knee joints were painful upon musculoskeletal testing. All joints were still able to move actively and passively. There was a slight restriction on the knee and wrist joints. Exams of his abdomen, CNS, respiratory system, and CVS did not turn up anything unusual.

Based on the patient's medical history and physical examination, the differential diagnoses included pulmonary tuberculosis (TB) with poncet poly-arthritis; rheumatoid arthritis, brucellosis, lymphoma, connective tissue disorders, HIV, and AOSD were considered.

His Lab investigations were done. The results of the CBC with peripheral film revealed neutrophilic leucocytosis and normocytic normochromic anemia. He had liver profile derangements and raised CRP levels. The other investigations all came out normal (**Table 1**). The lateral sides of both of his knees had a slight fluid collection,

Table 1: Laboratory findings.

Investigations	Patient Lab Results	Normal Range
HB (g/dl)	10.7	13.5-17.5
MCV (fl)	88	80-100
TLC (/µ)	21,800	5,000-10,000
Neutrophils (%)	82	40-60
Lymphocyte (%)	13.6	20-40
Platelets (/µ)	437,000l	135,000-317000
C-reactive protein (CRP) mg/dl	147	< 0.3
Ferritin levels (ng/dl)	11757	30-300
Total bilirubin (mg/dl)	0.4	0.1-1.2

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Investigations	Patient Lab Results	Normal Range
Alanine aminotransferase (U/L)	368	4-36
Aspartate aminotransferase (U/L)	667	8 to 33
Alkaline phosphatase (IU/L)	161	44-147
Prothrombin time (seconds)	11.4	10-13
INR	1.3	≤ 1.1
BUN (mg/dl)	10	8-24
Creatinine (mg/dl)	0.7	0.7-1.3
Na (mmol/L)	137	136-145
K (mEq/L)	3.8	3.5-5.2
Cl (mmol/L)	99	96-106
TSH (mIU/L)	0.77	0.5-4.15
MPICT	Negative	----------
Dengue NS1	Negative	----------
HBsAg	Non-reactive	----------
Anti Hcv	Non-reactive	----------
HIV serology	Negative	----------
Brucella antibodies	Negative	----------
RA factor	Negative	----------
Anti-CCP	Negative	----------
Anti-ds-DNA	Negative	----------
ENA	Negative	----------
AFB smear/Gene Xpert	Not detected	----------
Blood culture	No growth	----------
Urine culture	No growth	----------
Echo	Unremarkable	----------

Table 2: Laboratory Investigations after 3 weeks of prednisolone and Methotrexate therapy.

Investigation	Patient's Lab Results	Normal Range
HB (g/dl)	11.2	13.5-17.5
TLC (/µl)	9.2	5,000-10,000
Neutrophils (%)	62	40-60
Lymphocytes (%)	17	20-40
C-reactive protein (mg/dl)	12	< 0.3
Ferritin levels (ng/dl)	650	30-300
Total bilirubin (mg/dl)	0.5	0.1-1.2
Alanine aminotransferase (U/L)	62	4-36
Aspartate aminotransferase (U/L)	59	8 to 33
Alkaline phosphatase (IU/L)	124	44-147

revealed by knee ultrasonography. His blood and urine cultures came out negative. To rule out our differential diagnosis, special lab tests were performed. His serum ferritin levels were examined and found to be extremely elevated. Based on the Yamaguchi criteria and with a total of seven positive scores, a diagnosis of AOSD was made, after exclusion of all other differentials. Prednisolone (1mg/kg/day), Methotrexate (single oral dose of 5 mg/week), and NSAIDs were prescribed for the patient, and these medications significantly reduced his joint discomfort and fever. Upon follow-up after 3 weeks, his symptoms and lab parameters had improved (**Table 2**).

DISCUSSION

Epidemiology

The prevalence of AOSD is estimated to be one per 100,000 people, making it an extremely rare disorder. There are two peaks in its bimodal age distribution, the first peak affecting persons between the ages of 15 to 25 and the second peak affecting people between the ages of 36 to 46 years [5]. The ratio of women to men was found to be 2:1 in 125 cases of Japanese patients with AOSD studied by Wakai *et al.* in 1997 [6]. In a retrospective study conducted in 2009, 84 patients from Turkey were reviewed, 70.2% of them were women and 29.8% were men. The researchers concluded that AOSD usually affects women [7]. In 2015, 75 patients from China with AOSD had their demographic profiles, medical presentations, and laboratory findings examined. The chronological age range at the onset of AOSD was found to be 16–82 years, with a median age of 35.75±13.25 years. Men were less affected than women [8]. We describe 25 year old male.

Pathophysiology

The etiology and pathogenesis of AOSD, an extremely uncommon systemic auto-inflammatory disease, are still not entirely known. The occurrence of the condition has been linked to several factors, including genetics, immunological dysfunction, and bacterial and viral infections. Interleukins (IL-1, IL-6, and IL-18), macrophage-colony-stimulating factor, interferon-gamma (INF-g), and tumor necrosis factor-alpha (TNF-a) were all found to have significant roles in the etiology of AOSD in several researches [9].

Clinical Features

High spiking fever, throat discomfort, pain in the joints, salmon-color skin rash, and enlarged liver and spleen are clinical manifestations of AOSD. Some individuals, however, could only have a fever when they first appeared. These individuals might then undergo testing for fever of undetermined etiology (FUO) [10]. Research conducted in Thailand looked at 16 instances of AOSD, and all of them experienced arthralgia [11]. Hepatosplenomegaly and skin rashes were missing in our patient. Our patient reported a history of sore throat, high spiking fever, pain in multiple joints, and cervical lymphadenopathy.

Laboratory and Radiological Investigations

The most frequent abnormalities in AOSD laboratory results are leucocytosis (primarily neutrophils), anemia, high ferritin, CRP, ESR, as well as abnormal LFTs (AST and ALT). Serum ferritin levels are one of the laboratory abnormalities that are fivefold or above normal thresholds (often >1,000 ng/mL), and they are believed to be associated with cytokine release [12]. Our patient also had neutrophilia with raised TLC, elevated ferritin levels, anemia, increased ESR, CRP, and abnormally raised AST and ALT levels. Radiological investigations were non-specific in our patient except for a collection of fluid on the lateral aspect of both knee joints revealed by knee ultrasonography.

Diagnostic Criteria

Yamaguchi proposed his criteria for the diagnosis and categorization of AOSD in 1992 [13] (**Table 3**).

Table 3: Yamaguchi criteria for diagnosing adult-onset still disease.

Major Criteria	• Fever of 39°C more lasting longer than one week. • Arthralgia lasting longer than two weeks. • A maculopapular rash that is salmon in color. • Leucocytosis (more than 10,000/L and 80% or more granulocytes).
Minor Criteria	• throat pain/discomfort. • Splenomegaly or lymphadenopathy. • liver function derangements. • Negative ANA and RA factor.

The diagnosis of AOSD requires the fulfillment of five criteria, including two major ones.

Based on the Yamaguchi criteria, our patient had a total of seven positive scores because he had a high spiking fever, arthralgia, history of a sore throat, neutrophilic leucocytosis, lymphadenopathy, liver function abnormalities, and negative results for ANA and RA factor, with absence of skin rash and Splenomegaly.

Differential Diagnosis

As AOSD is an exclusionary condition, we assessed our patient for Tb with poncet poly-arthritis, urinary tract infection, typhoid, infective endocarditis, rheumatic heart disease, hepatitis B and C, HIV, connective tissue disorders, brucellosis, malaria, dengue fever, and malignancies. All inquiries turned up nothing. After that, we made our diagnosis of AOSD by applying Yamaguchi criteria.

Management

Anti-inflammatory drugs, such as steroids, NSAIDs, and anti-rheumatic medicines, are the mainstay of AOSD treatment. According to two studies, between 4 to 82% of patients are unable to control their AOSD symptoms with NSAIDs alone. 20% of the subjects in the studies reported experiencing negative effects. With more effectiveness in systemic AOSD, steroid medications are found to be successful in about 65% of patients, while methotrexate and other anti-rheumatic drugs (DMARDs) control the disease in 40-70% of AOSD cases who were taking steroids [14]. With the use of analgesics, steroids, and methotrexate, we effectively treated our patient and saw a significant improvement in his symptoms. The management of refractory patients of AOSD with recently developed biological agents has been proven to be successful in addition to DMARDs [15].

CONCLUSION

Adult onset still disease is an extremely uncommon condition. It can be difficult to identify AOSD because it is an exclusionary condition. Multimodal assessment, a thorough examination, and extensive laboratory investigations are required for its diagnosis.

CONSENT FOR PUBLICATION

Informed consent was taken from the patient for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

This study was designed and developed by BA, MTA, SMK, and ML. SB and HL conducted their preliminary literature review. MTA and SMK were in charge of data gathering, assembly, and patient evaluation. The manuscript was written by ML and BA. The last critical review and changes were completed by MTA and SMK. On behalf of all other authors, ML is the corresponding author.

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