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# Adult-Onset Still's Disease: Still a Serious Health Problem (a Case Report and Literature Review)

Authors' Contribution:
Study Design A
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Data Interpretation D
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**Conflict of interest:** None declared

**Patient:** Female, 53
**Final Diagnosis:** Adult-onset Still's Disease
**Symptoms:** Abdominal pain • fever
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Rheumatology

**Objective:** Rare disease

**Background:** Adult-onset Still's Disease (AOSD) is a rare systemic inflammatory disease accompanied by a triad of spiking fever, maculopapular exanthema, and arthralgia. To date, there is no definite laboratory or imaging test available for diagnosing AOSD, and the diagnosis is one of exclusion, which can be very challenging.

**Case Report:** We report on the case of a 53-year-old female who presented with fever, arthralgia, and abdominal pain. Her initial laboratory tests showed elevated AST and ALT, and normal leukocytes with bandemia. During her hospitalization, we evaluated the patient for other potential differential diagnoses. After an extensive workup, the patient was diagnosed with AOSD based on Yamaguchi criteria. Her serum ferritin levels were measured and found to be markedly elevated, which is a non-specific finding in AOSD patients.

**Conclusions:** This case highlights the important role of a detailed history and physical examination for timely diagnosis of AOSD to prevent complications and improve patient's prognosis.

**MeSH Keywords:** Abdominal Pain • Arthralgia • Exanthema • Ferritins • Still's Disease, Adult-Onset

**Full-text PDF:** http://www.amjcaserep.com/abstract/index/idArt/901846

## Background

In 1897, Dr. Still evaluated 22 children with arthritis in the UK and named the condition "juvenile rheumatoid arthritis" [1]. In 1971, Dr. Bywaters evaluated 14 adult patients with clinical manifestations resembling juvenile rheumatoid arthritis: macular rash, joint pain, and spiking fever [2]. This triad is now known to be characteristic of Adult-onset Still's Disease (AOSD). However, to date, there is no definite laboratory or imaging test available for diagnosing AOSD. Serum ferritin levels in AOSD patients are usually elevated, which is thought to be associated with cytokines dysregulation [3]. AOSD is an exclusion diagnosis; clinician's with a suspicion of AOSD, must rule out other medical conditions with similar manifestations including autoimmune diseases [4].The treatment for AOSD includes anti-inflammatory agents (non-steroid anti-inflammatory drugs (NSAIDs) and corticosteroids), immune-suppressants, and rheumatologic agents (methotrexate, azathioprine, tacrolimus, and cyclosporine). Intravenous immunoglobulins (IVIGs) could be used to treat an acute AOSD presentation [5]. Anti TNF-α and anti-interleukins have also been shown to be beneficial in treatment of refractory AOSD [6,7].

## Case Report

A 53-year-old female, originally from Puerto Rico, was admitted to our community hospital after experiencing spiking fevers with maximum temperature of 103°F (39.4°C) for more than two weeks, accompanied with loose stools, abdominal pain, decreased appetite, and generalized joint pain. The patient had a past medical history that was significant for anxiety, depression, type 2 diabetes, nodular goiter, dyslipidemia, gastroesophageal reflux disease (GERD), asthma, and fibromyalgia. She also reported experiencing some pruritic non-blanching rashes over the flexor aspect of both upper extremities as well as the medial aspect of her thighs a week prior to admission, which had resolved spontaneously. She denied any headaches, runny nose, cough, or shortness of breath. The patient lived alone, had no pets, and did not work. She was a former smoker but denied any alcohol or drug abuse. There was no history of incarceration or homelessness.

Upon admission, she was stable, and her temperature was 99.5°F (37.5°C). On physical examination, she had an enlarged spleen which was painful on palpation; splenomegaly was later confirmed by an imaging study (CT-scan). Her initial hematologic tests showed normal WBC count with bandemia (24.5%). Serum BUN and creatinine (Cr) levels were slightly elevated compared with her baseline values (13, 1.09 mg/dL *vs.* 11, 0.74 mg/dL) and her initial liver function tests were significant for slightly elevated AST (94 IU/L). ALT was within normal limits (33 IU/L) upon admission but became abnormal two days later. Interestingly, ANA and rheumatoid factor (RF) were negative. Laboratory tests for *Clostridium difficile* infection, salmonella infection, shigellosis, Lyme disease, babesiosis, ehrlichiosis, and HIV/AIDS were unremarkable. Computed tomography (CT) of the abdomen and pelvis was significant for splenomegaly and fatty liver.

Since the patient was diabetic and obese (BMI >30 kg/m$^2$), and her prominent complaint was abdominal pain, surgical consultation was done to rule out cholecystitis, diverticulitis, and other surgical related conditions. Also, broad-spectrum empiric antibiotic therapy was started for the patient, given a concern for intra-abdominal infection. Colonoscopy was performed as part of the abdominal pain evaluation and demonstrated a small polyp in the transverse colon which was excised. There was no evidence of any diverticulitis.

During hospitalization, the patient experienced intermittent high fevers (>39.4oC) and her rashes reappeared, so our hospital infectious disease specialist re-evaluated her. This time, on physical examination, she had multiple non-blanching salmon colored rashes over her left thigh as well as arthritis in her fingers with swollen interphalangeal joints. On further history investigation, the patient reported experiencing a sore throat a week before initiation of other symptoms.

Given the new findings in her history, persistent fever, arthritis, and rashes, the possibility of AOSD was raised and serum ferritin levels were ordered; and revealed highly elevated levels (2,723 ng/mL). We discontinued the empiric antibiotics and started prednisone (20 mg twice a day) for the patient. Subsequently, her joint pain began to improve. However, she continued experiencing fever (102.2°F, 39°C). The patient was then referred to another institute for further rheumatology investigation and workup, where a PET scan showed diffuse supraclavicular, mediastinal, and hilar lymphadenopathy. An excisional cervical lymph node biopsy revealed reactive lymphadenopathy. These new findings confirmed our diagnosis of AOSD. The patient's symptoms started to improve by the time the biopsy was performed. Prednisone was held and a six-week follow-up was recommended.

## Discussion

### Epidemiology

Adult-onset Still's disease (AOSD) is a rare disease. There are few published data available regarding its incidence and prevalence in different populations. In 2009, Owlia et al. from Iran reviewed more than 1,000 PubMed titles and reported that the crude prevalence of AOSD was 1.5 cases in 100,000–1,000,000. In the same review, the age of AOSD onset had a bimodal range

with two group: 15–25 and 36–46 years of age [8]. In 1997, Wakai et al. from Japan reviewed 125 cases of Japanese patients with AOSD and reported the female to male ratio was 2.1 [9]. In a 2009 retrospective study, 84 Turkish patients were evaluated, and 70.2% of them were female versus 29.8% male. The investigators concluded that AODS affects women more than men [10]. In 2015, the demographic features, clinical manifestations, and laboratory tests of 75 Chinese patients with AOSD were studied and the age range at the time of AOSD onset was reported to be 16–82 years with the median age of 35.75±13.25 years, and women were more affected than men (44 *vs.* 31) [11].

**Pathogenesis**

The pathogenesis of AOSD is not clear. Several factors have been suggested to contribute to the disease occurrence, including genetics, viral and bacterial infections, and immune dysfunction [12–15]. A number of studies reported an important role for interleukins (IL-1, IL-6, and IL-18), macrophage colony stimulating factor, interferon gamma (INF-γ), and tumor necrosis factor alpha (TNF-α) in AOSD pathogenesis [16–19]. In a recent study performed in South Korea, serum levels of CXCL10 and CXCL13 in 39 patients with active AOSD were significantly higher than in patients with rheumatoid arthritis and healthy people [20]. The investigators concluded that serum levels of CXCL10 and CXCL13 might be useful markers to assess AOSD activity.

**Clinical manifestations**

AOSD is a systemic inflammatory disease accompanied by spiking fever, sore throat, arthralgia, rash, and hepatosplenomegaly. However, some patients may present only with fever. These patients may then go under evaluations for fever of unknown origin (FUO) [21]. In addition to fever, our patient had a mild sore throat a week prior to her admission to our institution. Some studies have shown that pharyngitis could be an initial manifestation in AOSD [22,23]. Another characteristic of AOSD is salmon colored macular or maculopapular rash. The rash may be pruritic in its nature [24]. Another form of rash seen in AOSD is an urticarial eruption on the flexor surface of limbs or trunk [24–27]. Some studies reported that any cutaneous stimuli such as a scratch test could lead to an exaggerated urticarial response in patients with AOSD [28]. Our patient had a history significant for pruritic maculopapular rashes but was presented with fever, abdominal pain, and generalized joint pain. While she was hospitalized for further evaluation, the rash reappeared and she experienced arthralgia in multiple joints with interphalangeal joints more likely to be involved.

Joint pain (arthralgia) is another symptom of AOSD. In one study in Thailand, 16 cases with AOSD were reviewed and all of them had arthralgia (100%) [29]. In contrast, reviewing 75 cases with AOSD in China showed less incidence for arthralgia when compared with five other case reviews (57.3% in China *vs.* 96.4% in Turkey, 79% in Italy, 88.8% in France, and 97.5% in Spain) [11].

Our patient also presented with abdominal pain and on physical examination experienced tenderness on palpation over her spleen. Interestingly, although abdominal pain is considered to be one of the non-specific symptoms in AOSD, we only found one study reported it in 50% of the Japanese patients with AOSD [30]. Splenomegaly is another non-specific sign of AOSD. In a study by Liu et al., only 14 out of 72 patients (18.6%) with AOSD had splenomegaly [11]. Reactive hemophagocytic syndrome (RHS) is another life-threatening complication of AOSD. Fever, pancytopenia, liver dysfunction, coagulopathy, and neurologic symptoms are characteristics of RHS. In a retrospective study in South Korea, 109 cases with AOSD (21 patients with both RHS and AOSD) were evaluated for splenomegaly (from 1996 to 2013). Of those with AODS and RHS, 11 patients had splenomegaly (52%). In contrast, only 17 patients out of 88 patients with AOSD alone had splenomegaly (19.3%) [31]. Our patient had splenomegaly, elevated liver enzymes (AL and AST), and fever as positive signs for RHS but no pancytopenia and neurological symptoms. Other less common manifestations of AOSD include hepatomegaly [11,32,33], pneumonia and pleuritis [34], thrombotic thrombocytopenic purpura (TTP) [35], and cardiac involvement (pericarditis and tamponade) [36].

**Laboratory and imaging findings**

Laboratory findings in AOSD are similar to those in other inflammatory processes, with the most common abnormalities being: leukocytosis (mostly neutrophils), anemia, elevated ferritin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and abnormal liver function tests (AST and ALT) [31,37,38]. Among the laboratory abnormalities, serum ferritin levels are reported to be five times or more above the upper normal limits (usually >1,000 ng/mL in most cases) which is thought to be related to cytokines release [3]. Although some studies consider it as a diagnostic tool for AOSD [37,39], markedly elevated ferritin is not significant to AOSD. Other causes of highly elevated ferritin include systemic juvenile idiopathic arthritis and macrophage activation syndrome (MAS) [40]. Ferritin has several isoforms. Glycosylated ferritin is an isoform of ferritin which is generally low in patients with AOSD. In a retrospective study in 2001, serum ferritin and glycosylated ferritin levels of 49 patients with AOSD were compared with 120 controls. Patients with AOSD had significantly higher values of serum ferritin (4,752±9,599 *vs.* 1,571±3,807 ng/mL, $p<0.05$). In contrast, serum glycosylated ferritin levels were significantly lower in AOSD patients when compared with controls (15.9±11.9% *vs.* 31.5±18.7%, $p<0.001$) [39]. Our patient's serum ferritin levels were markedly elevated (2,723 ng/mL).

We did not measure her serum glycosylated ferritin levels. As in our case, ANA and RF have also been reported to be negative in patients with AOSD [41].

Imaging studies are usually unremarkable in patients with AOSD except for progressive erosions and narrowing joint space [41–43] and hepatosplenomegaly [43,44].

**Classification**

In 1992, Yamaguchi introduced his criteria for AOSD diagnosis and classification [4]. This criteria has been validated and reported to be the most sensitive criteria (93.5%) compared to Calabro, Cush, and Reginato criteria [45,46].

Yamaguchi criteria is divided into major and minor criteria:
Major criteria:
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:
1) Sore throat.
2) Lymphadenopathy and/or splenomegaly.
3) Liver dysfunction.
4) Negative rheumatoid factor (RF) and antinuclear antibody (ANA) tests.

Five features of Yamaguchi criteria, including at least two major criteria, must be present for AOSD diagnosis. Our patient had three major features of Yamaguchi criteria: fever, arthralgia, and rash. She also met three features of Yamaguchi minor criteria: history of a sore throat, splenomegaly, and negative RF and ANA.

There are a number of diseases that need to be excluded in the Yamaguchi classification before the diagnosis for AOSD can be made:
A) Infections: infective endocarditis, hepatitis B and C, rubella, HIV, cytomegalovirus, coxsackie, tuberculosis, and Lyme disease.
B) Malignancies: hematologic (lymphoma, leukemia), solid tumors (breast and lung cancers mostly), and melanoma [47].
C) Vasculitis: polyarteritis nodosa (PAN), granulomatosis with polyangiitis (Wegner's granulomatosis), and Takayasu's arteritis.
D) Connective tissue diseases: systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD)

We evaluated our patient for infections: tuberculosis, malaria, babesia, isospora, cyclospora, giardia, salmonella, HAV/HBV/HCV, CMV, EBV, typhoid, Lyme disease, ehrlichia, HIV, chlamydia, gonorrhea, syphilis, rotavirus, Yersinia, and campylobacter infections; all were unrevealing.

Biopsy of lymph nodes, stomach, colon, and thyroid nodule in our patient were unremarkable for malignancies. Hepatobiliary (HIDA) scan showed normal radiotracer distribution throughout the liver, common bile duct, and small bowel. Transthoracic echocardiography (TTE) was unremarkable for infective endocarditis. Immunostaining of the cervical lymph node specimen did not reveal any IgG4 related changes. Taken together, the immunostaining along with the flow cytometry results showed a reactive process. No granulomas or malignancy changes were seen.

Since the patient's fever, arthralgia, rash, and lymphadenopathy were improved significantly after several days of hospitalization and she was willing to leave the hospital, we recommended that she follows up for further dermatologic and rheumatologic evaluation. In the meanwhile, we made the AOSD diagnosis based on the Yamaguchi criteria which is, to our knowledge, the most sensitive criteria available for AOSD diagnosis.

**Treatment**

AOSD treatment is based on anti-inflammatory medications, including steroids, NSAIDs, and anti-rheumatic agents to control symptoms such as fever, joint pain, and systemic inflammation [5]. Two studies showed that NSAIDs alone are not effective to control AOSD symptoms in 4–82% of patients. In those studies, 20% of patients complained of adverse effects [48,49]. Corticosteroids are reported to be effective in approximately 65% of patients [50] with greater efficacy in systemic AOSD [49], while methotrexate and other anti-rheumatic agents (DMARDs) control the disease in 40–70% of the steroid-dependent AOSD cases [49]. Some retrospective studies suggest that cyclosporine is as effective as methotrexate in systemic AOSD [49,50]. Cyclosporine could be used in patients with severe AOSD as well as patients with microphage activation syndrome (MAS) [50–52]. MAS is a complication of AOSD which is thought to be caused by long-standing hyperactivity of immune system with dysregulated $CD_8^+$T cells and macrophages expansion [51,52].

Anti-interleukin 1 (IL-1Ra and anakinra) [38], anti-interleukin 6 (tocilizumab) [53], anti- IL1β (canakinumab) [54], and TNF-α inhibitors (infliximab, etanercept, and adalimumab) [55] are other newly developed biological treatments which have been shown to be effective in refractory AOSD [6,7]. Overall, either monotherapy or combination therapy can be used to treat AOSD based on the disease course and symptoms severity.

**Prognosis**

AOSD is a disease with a number of distinct clinical patterns, each with significant prognostic consequences [41,43,56]:

1) The disease can be self-limited (monocyclic) in nature. This pattern is characterized by fever, rash, and organomegaly. Remission happens within one year from the onset of the first (and last) episode of the disease.
2) The disease may have an intermittent (polycyclic systemic) pattern with several flare-up episodes with or without joint involvement. Patients may experience a complete remission between the flares and episodes may be several years apart and/or tend to be milder than the initial episode.
3) The disease may have a chronic articular pattern. In this pattern, the articular manifestations (joint involvements) are dominant and may range from mild to severe symptoms which may lead to joint destruction.

In general, patients with only localized disease have a better prognosis compared to those with more disseminated disabilities and/or severe complications such as pericarditis, diffuse intravascular coagulation (DIC), and liver and respiratory failure.

## Conclusions

AOSD is an exclusion diagnosis which can be very challenging. It needs an extensive workup and multidisciplinary evaluation to rule out infections and hematologic-oncologic processes. Since the disease has a number of life-threatening complications, a detailed history and physical examination are needed for patients with FUO when there is a suspicion for AOSD to prevent complications and improve the prognosis. Our patient experienced a flare-up with her rash reappearing and interphalangeal joints involvement while she was under evaluation for fever and abdominal pain. This suggests that caregivers should be aware of newly developed symptoms and/or signs in hospitalized patients in order to address them properly and on time.

On the other hand, despite having access to many imaging technologies these days, a detailed history and a good physical examination are still two powerful tools which can guide us through an accurate diagnosis.

More clinical studies could be useful to increase our knowledge about AOSD and guide us through tailoring more effective therapies.

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