# Adult-onset Still's Disease

Shrestha KH, Nikhil OM, Paudyal P, Kharel P

Department of Internal Medicine,
National Academy of Medical Sciences,
Bir Hospital,
Mahaboddha, Kathmandu, Nepal.

**Corresponding Author**
Krishna Hari Shrestha
Department of Internal Medicine,
National Academy of Medical Sciences,
Bir Hospital,
Mahaboddha, Kathmandu, Nepal.
E-mail: krishastha14@gmail.com

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## ABSTRACT

Adult-onset Still's disease (AOSD) is a rare auto inflammatory condition characterized by high fever, joint pain, a transient salmon-colored rash, and elevated ferritin levels. Its diagnosis is primarily clinical, relying on the exclusion of infections, malignancies, and other autoimmune disorders.

A 23-year-old woman presented with intermittent high fever, polyarthralgia, and a fleeting salmon-pink rash. Laboratory results showed neutrophilic leukocytosis, elevated ESR, CRP, and ferritin (1650 ng/mL), along with mild liver enzyme elevation and negative ANA/RF tests. Extensive investigations for infections and cancer were inconclusive. She met the Yamaguchi criteria for Adult-onset Still's disease.

The patient responded well to oral prednisolone and methotrexate. After a relapse at 7 months, treatment was adjusted with increased methotrexate doses, a short course of steroids, and NSAIDs. At a one-year follow-up, she remains symptom-free, with normalized ferritin levels (280 ng/mL) and no signs of macrophage activation syndrome (MAS).

Adult-onset Still's disease should be considered in patients with fever of unknown origin accompanied by systemic inflammation. Early recognition and immunosuppressive therapy can lead to remission, even in settings with limited resources.

## KEY WORDS

*Adult-onset still's disease, Fever, Methotrexate*

## INTRODUCTION

Still's disease was first identified by G. F. Still in 1897 in children, now known as Systemic Juvenile Idiopathic Arthritis. Later, Eric Bywaters described similar cases in adults, distinguishing adult-onset Still's disease (AOSD) as a separate condition, rather than simply an age-related form of juvenile polyarthritis.[1] The crude annual incidence of AOSD is estimated to be 0.16–0.22 per 100,000 population.[2,3]

AOSD is an inflammatory disorder of unknown origin, often presenting with high spiking fevers, joint pain, and a transient rash. Additional common symptoms include sore throat, hepatosplenomegaly, swollen lymph nodes, and serous membrane inflammation.[4]

The pathogenesis of AOSD involves dysregulated innate and adaptive immunity, with an overproduction of pro-inflammatory cytokines. Innate immune cells such as macrophages and neutrophils play a central role in disease progression. Dendritic cells, neutrophils, NK cells, macrophages, and lymphocytes recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) via their Toll-like receptors (TLRs), triggering intracellular immune responses. Neutrophil activation is particularly significant, as the secretion of enzymes and antimicrobial proteins contributes to the initiation and persistence of inflammation.[5,6] Here, we present the case of a 23-year-old female patient diagnosed with AOSD, who has achieved remission.

## CASE REPORT

A 23-year-old woman with no known comorbidities presented with a one-month history of intermittent high fever and multiple joint pains. The fever, which spiked daily in the evening, reached a peak of 103°F but was not associated with chills or rigors. She also experienced insidious onset of joint pain, predominantly affecting her wrists, fingers, and elbows. The pain was described as dull, aching, non-radiating, and moderate in intensity. Additionally, she reported occasional headaches and erythematous, non-itchy rashes over her upper chest and forearms that were transient in nature.

Her medical history was notable for the absence of sore throat, photosensitivity, oral or genital ulcers, alopecia, Raynaud's phenomenon, morning stiffness, weight loss, cough, dyspnea, chest pain, hematuria, or any previous similar episodes. There was no family or personal history of autoimmune or rheumatologic disorders, and she had not recently taken any medications or experienced insect bites.

Before presenting to our Hospital, she had been treated with multiple antibiotics, including a three-day course of ceftriaxone, followed by tazobactam-piperacillin and levofloxacin for five days. Upon presentation, she was alert, oriented, and had stable vital signs. A physical examination revealed a firm, mobile, non-tender left supraclavicular lymph node measuring approximately 1.5 X 1 cm, with no overlying skin changes. Musculoskeletal examination showed tenderness over her wrists, interphalangeal joints, ankles, and shoulders, but there was no visible swelling or erythema. Respiratory, cardiovascular, abdominal, and neurological exams were unremarkable. A skin exam revealed multiple salmon-pink, blanchable macules on her anterior chest and forearms, coinciding with febrile episodes. There were no signs of pharyngeal erythema or oral ulcers.

Initial laboratory tests revealed a hemoglobin of 9.5 g/dL, a total leukocyte count of 14,700/$mm^3$ (with neutrophilic predominance), and a platelet count of 392,000/$mm^3$. Renal function and serum electrolytes were normal. Liver function tests showed mild elevations in AST (32 U/L) and ALT (37 U/L), with normal bilirubin levels. Blood, sputum, and urine cultures were negative, and tests for tuberculosis, malaria, dengue, scrub typhus, leptospirosis, kala-azar, and brucellosis also yielded no abnormalities. A peripheral blood smear showed normocytic normochromic RBCs with neutrophilia, and inflammatory markers were significantly elevated, including ESR (50 mm/hr), CRP (191 mg/L), and serum ferritin (1650 ng/mL). LDH was elevated at 1930 U/L. Urinalysis revealed mild albuminuria but no active sediment. Rheumatoid factor (RF), anti-CCP, and ANA were all negative. Chest and wrist X-rays, as well as echocardiography, were normal. Contrast-enhanced CT scans showed mild splenomegaly and supraclavicular and mediastinal lymphadenopathy. An excisional biopsy of the cervical lymph node confirmed reactive lymphadenitis with no evidence of granulomas, necrosis, or atypical cells. Bone marrow aspiration revealed a hypercellular marrow without atypical cells, and bone marrow cultures showed no growth.

Given her clinical presentation and lab results, the patient was diagnosed with Adult-Onset Still's Disease (AOSD) based on the Yamaguchi criteria, which requires meeting at least five criteria, with a minimum of two major criteria. The major criteria she met included high spiking fever (≥ 39°C for ≥1 week), arthralgia lasting over two weeks, and leukocytosis with neutrophilia. The minor criteria included lymphadenopathy (supraclavicular and mediastinal), mild splenomegaly, mildly elevated liver enzymes, and negative RF and ANA. With three major and four minor criteria fulfilled, AOSD was diagnosed.

She was initially treated with oral prednisolone (1 mg/kg/day) and NSAIDs(Naproxen). She became afebrile within two days, and her leukocyte count dropped to 5,480/$mm^3$ by the fourth day. Methotrexate (10 mg weekly) was added on day four, and she was discharged with follow-up plans. Over time, her prednisolone dose was tapered within one and half month, NSAIDs were discontinued, and methotrexate was increased to 15 mg weekly. She remained asymptomatic during follow-up.

At the 7-month follow-up, she presented again with a recurrence of fever and joint pain lasting two weeks. Treatment was adjusted with a short course of prednisolone and NSAIDs, and methotrexate was increased to 20 mg weekly. Her symptoms improved, and treatment was continued. At the one-year follow-up, she was symptom-free, with no new complaints of fever or joint pain. Her ferritin levels had normalized to 280 ng/mL, ESR 13 mm/hr and CRP 3 mg/dl and there were no signs of neutrophilia, cytopenia, or liver function abnormalities.

## DISCUSSION

Adult-Onset Still's Disease (AOSD) is an inflammatory condition that often presents with fever of unknown origin. The disease manifests variably, typically with high-grade fever, arthralgia, a transient rash, lymphadenopathy, and hepatosplenomegaly.[7] Yamaguchi et al. established diagnostic criteria for AOSD, which include four major criteria fever, arthralgia, characteristic rash, and leukocytosis and four minor criteria sore throat, lymphadenopathy/splenomegaly, abnormal liver function tests, and negative rheumatoid factor (RF) and antinuclear antibody (ANA). A diagnosis is confirmed by meeting at least five criteria, with a minimum of two major criteria, providing a sensitivity of 96.2% and specificity of 92.1%.[8] In this case, the diagnosis of AOSD was established based on three major and four minor criteria after ruling out other potential causes.

AOSD can lead to complications such as pericarditis, myocarditis, serositis, hepatic failure, and involvement of the pulmonary or nervous systems, none of which

were seen in this patient.[9] Life-threatening complications like disseminated intravascular coagulation (DIC), hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome (MAS) occur in up to 15% of patients.[10]

Laboratory results typically show significant elevations in erythrocyte sedimentation rate (ESR) and leukocytosis, predominantly neutrophils.[11] Elevated serum ferritin levels, found in about 70% of AOSD cases, are considered a hallmark of the disease. This is believed to result from cytokine-driven stimulation of the reticuloendothelial system or hepatic injury.[12] In this case, the patient exhibited elevated ESR, neutrophilic leukocytosis, and markedly high serum ferritin, along with mild hepatic dysfunction common features in AOSD.[13]

While NSAIDs or aspirin are often used initially to manage symptoms, they are largely ineffective in AOSD.[14] Corticosteroids remain the first-line treatment, particularly in patients presenting with pericarditis, serositis, anemia, or significantly elevated liver enzymes. This patient showed improvement with prednisolone therapy, which was later tapered.[15] For patients who do not respond adequately to corticosteroids or for those requiring steroid tapering to avoid relapses, disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, are commonly used. Our patient responded well to methotrexate, which was escalated during relapse, and she remains in remission.[16]

Relapse in AOSD occurs in 30% to 50% of patients and is typically managed by increasing glucocorticoid doses, adjusting immunosuppressant regimens, or initiating biologic agents.[17,18] This patient experienced a relapse seven months after her initial remission, which was successfully managed by increasing her methotrexate dose from 15 mg to 20 mg weekly, along with a short course of prednisolone. She remained in remission thereafter, demonstrating the effectiveness of traditional DMARD-based treatments in the appropriate patient population.

Given the risk of macrophage activation syndrome (MAS) in AOSD patients, we closely monitored her blood counts, liver function, and serum ferritin during both her initial presentation and relapse. At no point did she show signs of cytopenia, transaminitis, or an additional rise in ferritin, effectively ruling out MAS throughout her disease course.

For patients who do not respond to conventional treatments like corticosteroids and DMARDs, biologic agents should be considered. As pro-inflammatory cytokines such as TNF-alpha, interleukin-1, and interleukin-6 play a key role in AOSD pathogenesis, cytokine blockers like anakinra and tocilizumab have shown efficacy in severe or treatment-resistant cases.[19]

## CONCLUSION

Adult-onset Still's Disease remains a challenging diagnosis due to its nonspecific symptoms that can mimic infections, malignancies, and other rheumatic diseases. This case underscores the importance of recognizing the classic triad of fever, transient rash, and arthralgia, alongside specific biomarkers like hyperferritinemia (> 1,000 ng/mL) and neutrophilia, to expedite diagnosis using the Yamaguchi criteria. Early treatment with corticosteroids and methotrexate can lead to prolonged remission, even in resource-limited settings, although relapses (which occur in 30-50% of patients) may require intensifying treatment with DMARDs. The use of methotrexate offers a cost-effective strategy for maintaining remission in the absence of biologic agents. Raising awareness of AOSD's diverse presentations and initiating early immunosuppressive therapy are critical in reducing morbidity and improving long-term outcomes.

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