DOI: 10.7860/JCDR/2026/82277.22388

Case Report

Internal Medicine Section

Adult-onset Still's Disease without Elevation of Erythrocyte Sedimentation Rate, C-reactive Protein or Serum Ferritin: A Case Report

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ABSTRACT

Fever accompanied by arthralgia and rash has multiple differential diagnoses. It often resembles a viral exanthem and is treated accordingly. However, certain clinical and laboratory features may suggest a specific diagnosis. Here, authors present the case of a 19-year-old male who had fever, polyarthralgia, throat pain, and pinkish rashes. The rashes appeared with the onset of fever and resolved when the fever subsided. He was initially treated for a viral exanthem, with bacterial infection considered in the differential diagnosis. As he did not respond to standard fever management, proceeded to exclude specific infections, malignancy, and autoimmune conditions. After a thorough evaluation, he was diagnosed Adult-Onset Still's Disease (AOSD), which responded well to oral corticosteroids. AOSD is an autoinflammatory disorder with systemic manifestations characterised by high spiking fevers, polyarthralgia, and a typical salmon-pink rash. The rash is usually non pruritic, macular or maculopapular, and often coincides with febrile episodes. It is one of the differential diagnoses in Pyrexia of Unknown Origin (PUO), warranting appropriate and comprehensive evaluation. Classically, AOSD demonstrates elevated inflammatory markers, particularly serum ferritin. Interestingly, index patient had normal values of all three inflammatory markers {Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and serum ferritin} despite having an inflammatory disease, which makes this presentation rare in an already uncommon condition. This report indicates that AOSD can present without a typical rise in inflammatory markers, creating a diagnostic dilemma. Only strong clinical suspicion may lead to an accurate diagnosis.

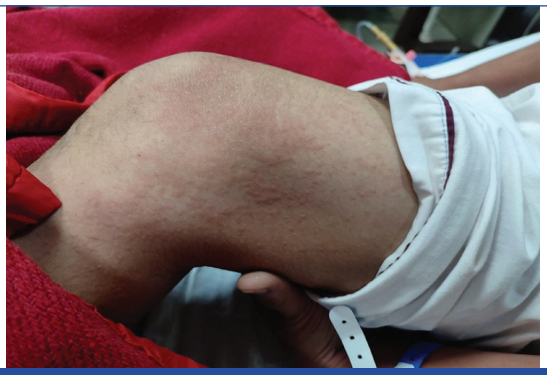
Keywords: Arthralgia, Fever, Inflammatory marker, Rash

CASE REPORT

A 19-year-old male was admitted with fever for 12 days, associated with chills and rigors. The temperature ranged from 99°F to 102.5°F. There was no specific diurnal variation. He reported diffuse small and large joint pains along with generalised body aches. He also noted pink, maculopapular, non pruritic rashes on the trunk and limbs, sparing the palms, soles, and oral mucosa [Table/Fig-1,2]. Additionally, he had a sore throat and painful swallowing. There were no other organ-specific complaints. On general examination, he was hypotensive (blood pressure 90/60 mmHg) and tachycardic (pulse rate 111 beats per minute). Throat examination revealed posterior pharyngeal congestion. Although he reported multiple joint pains, there was no joint stiffness, redness, or swelling. He had no history of drug or food allergies. His vaccination status was up to date.

He reported a similar episode one month earlier, with fever, pink rash, and arthralgia. At that time, he consulted a physician and was prescribed oral azithromycin 500 mg once daily for three days and paracetamol 500 mg thrice daily. Due to arthralgia, he also received naproxen 500 mg twice daily for two days, which resolved his symptoms. Dengue testing at that time was negative. A complete blood count showed leukocytosis (total leukocyte count 15,000/cmm with 91% neutrophils). ESR was 10 mm in the first hour, and CRP was 0.06 mg/dL.

Because this was the second similar episode within a month, the differential diagnoses included viral fever, streptococcal infection, rickettsial fever, infective endocarditis, erythema multiforme, chikungunya, and autoimmune disease. Consequently, an extensive work-up was performed, including complete blood count, liver and renal function tests, inflammatory markers, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), urine and blood cultures, and a fever profile (malaria, dengue, chikungunya, scrub typhus) [Table/Fig-3].



[Table/Fig-1]: Showing maculopapular pinkish rash lower limb.

[Table/Fig-2]: Showing maculopapular, pinkish rash on upper limb.

He was started on intravenous cefepime 1 g 12-hourly, intravenous fluids, tablet paracetamol 650 mg 8-hourly, and tablet fexofenadine 180 mg once daily. Complete haemogram showed leukocytosis (16,720/cmm) with neutrophilia (89%), while other parameters were normal. Liver function tests were mildly deranged (aspartate transaminase 45 U/L and alanine transaminase 56 U/L). Renal function and serum albumin levels were within normal limits. Urine

Parameters	Reports	Normal
Haemoglobin (gm/dL)	13.5	11.5-16.5
Total leukocyte count (/cumm)	16720	4000-11000
Neutrophil (%)/lymphocyte (%)/monocyte (%)/eosinophil (%)/basophil (%)	89/6/5/0/01	60-70/30-40/2-8/1-6/0-1
Platelet count (/cumm)	1,30000	1,50000-4,50000
Serum bilirubin (mg/dL)	0.8	0.2-1
Aspartate Transferase (AST) (U/L)	45	0-45
Alanine Transferase (ALT) (U/L)	56	0-35
Alkaline Phosphatase (ALP) (U/L)	110	53-141
Serum creatinine (mg/dL)	0.9	0.5-1.5
Serum sodium (mEq/L)	135	135-146
Serum potassium (mEq/L)	4.4	3.5-5.5
C-reactive Protein (CRP) (mg/dL)	0.78	0.08-0.79
Erythrocyte Segmentation Rate-ESR (Westergren) (mm 1st hour)	03	2-12
Serum albumin (gm/dL)	4.2	3.5-5.2
Serum ferritin (ng/mL)	322.50	23.9-336.2
Procalcitonin (ng/mL)	0.24	0.02-0.3
Dengue card test	Negative	-
Malarial kit test	Negative	
Chikungunya serology	Negative	
Serum lactate dehydrogenase (U/L)	193	208-378
Creatine phosphokinase (U/L)	110	120-200
ASO titer (IU/mL)	200	0-200
IgM Scrub typhus	Negative	-
Rheumatoid arthritis factor	Negative	
Anti-cyclic citrullinated peptide	Negative	
Urine routine	Normal	
Urine culture	Sterile	
Blood cultures	Sterile	
Epstein-Barr Virus-DNA-PCR	Negative	
CMV-DNA-PCR	Negative	
HIV by ELISA	Non reactive	
Hepatitis B surface antigen	Non reactive	
Anti Hepatitis C Antibody	Non reactive	
Chest roentgenogram posteroanterior view	Normal	
Abdomen sonogram	Normal	
Contrast enhanced Computed tomogram (Abdomen with pelvis and thorax)	Normal	
Echocardiogram	No clot or vegetations	

[Table/Fig-3]: Investigations.

examination did not reveal pus cells, red blood cells, casts, or proteinuria. He had normal levels of inflammatory markers (ESR, CRP, serum ferritin, and procalcitonin). His test results were negative for malaria, dengue, chikungunya, scrub typhus, and urinary and bloodstream infections.

Even after 72 hours of inpatient treatment and persistent fever without a definite diagnosis, additional investigations were performed. These included Contrast-Enhanced Computed Tomography (CECT) of the abdomen, pelvis, thorax, and neck; echocardiography; viral serology (Epstein-Barr virus, cytomegalovirus, hepatitis B surface antigen, hepatitis C, and human immunodeficiency virus); and antinuclear antibody (ANA) testing by ELISA. No abnormalities were identified on imaging. Viral serology was non reactive, and ANA was negative.

As there was no clinical improvement, and considering the possibility of multidrug-resistant microorganisms, antibiotics were escalated to intravenous piperacillin-tazobactam 4.5 g 8-hourly and oral doxycycline 100 mg twice daily.

He remained febrile even on day 3 after escalation of antibiotics. In view of persistent fever, continuous arthralgia, pink rash, and after ruling out infectious, autoimmune, rheumatologic, and malignant causes, he was finally diagnosed with AOSD based on Yamaguchi's criteria [Table/Fig-4] and was started on oral prednisolone 50 mg per day [1]. His fever subsided two hours after starting steroids but fluctuated between 99°F and 100°F for the next two days. From the third day onward, he became afebrile, and his arthralgia and rashes resolved. Peripheral leukocytosis also normalised (total leukocyte count 4,840/cmm) by day 3 of oral steroid therapy. He was discharged on oral prednisolone 30 mg per day and ranitidine 150 mg once daily.

Major criteria	-Fever > 39°C -Arthralgia or arthritis, lasting 2 weeks or longer -Typical rash -Leukocytosis >10000/mm with > 80% polymorphonuclear cells
Minor criteria	-Sore throat -Recent development of significant lymphadenopathy -Hepatomegaly or splenomegaly -Abnormal liver function test -Negative tests for Antinuclear Antibody (ANA) and rheumatoid factor (IgM)
Exclusion criteria	-Infections -Malignancies -Other rheumatic diseases
Five or more criteria are required with 2 or more being major criteria for diagnosis of AOSD. Sensitivity 96.2% and specificity 92.1%	

[Table/Fig-4]: The Yamaguchi criteria [1].

One week after discharge, he attended outpatient follow-up, and repeat haemogram was normal. He was advised to taper oral steroids over the next two weeks and to return if symptoms recurred.

DISCUSSION

AOSD is often diagnosed late or misdiagnosed due to its clinical resemblance to many other inflammatory disorders such as viral or bacterial infections, autoimmune diseases, and malignancies including leukaemia, lymphoma, and metastatic disease. It is an autoinflammatory condition that may present with periodic fever, body aches, joint pain, sore throat, generalised rash, tissue inflammation, neutrophilic leukocytosis, and elevated inflammatory markers. Its annual incidence is 0.16 cases per 100,000 persons, with a female-to-male ratio of 3:2 [2]. The peak age of onset is 15-25 years and 36-46 years, and the disease may follow a monophasic, intermittent, or chronic course [3]. Various markers of inflammation include ESR, CRP, serum ferritin, glycosylated ferritin, leukocyte count, and procalcitonin. Although these markers indicate inflammation, none are specific enough to clearly differentiate between infectious and non infectious causes of inflammation [4].

However, a multifold rise in serum ferritin levels in the background of febrile episodes with typical rashes and arthralgia indicates some specific non infective diseases such as vasculitis, Macrophage Activation Syndrome (MAS), Systemic Lupus Erythematosus (SLE), AOSD, etc. Although AOSD was suspected, and inflammatory markers, particularly serum ferritin, were expected to be significantly high, the normal ranges of ESR, CRP, and serum ferritin placed us in a dilemma regarding the diagnosis. As he had similar features a month ago, and based on past and current investigation reports, possible infections, autoimmune diseases, and malignancy were excluded. This led us to diagnose AOSD based on the Yamaguchi criteria [1].

Its treatment options include corticosteroids, methotrexate, a Disease-Modifying Antirheumatic Drug (DMARD), Non Steroidal Anti-Inflammatory Drugs (NSAIDs), anakinra, etc. [5]. Index patient responded well to oral steroids, which were tapered over days. Although serum ferritin typically rises to more than five times the normal upper limit in AOSD, there are case reports in which serum ferritin remained within normal range [6,7].

An article from central Iran observed ESR and CRP to be raised in 100% of cases of AOSD, while serum ferritin was elevated in 71% [8]. In a Chinese study, ESR, CRP, and ferritin were elevated in 77%, 84%, and 74.1% of cases, respectively. However, these studies did not mention whether all three markers were within normal range in the remaining cases, or whether at least one or two markers were elevated [9].

Inflammatory markers are useful in supplementing the diagnosis, understanding the prognosis, suspecting conversion of primary disease into a complicated state such as MAS, and evaluating the response to treatment [10]. In fact, their high levels may be associated with increased mortality in patients with AOSD [11,12]. There are no significant differences in the clinical features of AOSD between patients with raised ferritin and those without, but literature review supports the crucial role of commonly used inflammatory markers in the semiology of AOSD [13].

There are several diseases in which inflammatory markers may remain within normal limits despite the presence of inflammation in their pathogenesis. Rheumatoid arthritis is a well-known inflammatory disease, but ESR and CRP may remain normal in its early phase in approximately 35-45% of cases [14]. Low CRP can be explained in Interferon-α (IFN-α)-related inflammation, such as in SLE. However, in diseases such as AOSD, helper T1 and helper T17 cells are elevated during active disease, contributing to the activation of macrophages and neutrophils by producing more IFN-γ and IL-17 [15,16]. Therefore, CRP should classically rise in type 2 IFN-γ-related inflammatory disease, but unexpectedly this was not the case in index patient.

Normal ESR and CRP in some cases of AOSD may be due to technical errors or recent NSAID use. There may also be less extensive inflammation leading to non detectable levels or only minor elevation, keeping values toward the high-normal range. These explanations may apply to index case as well, but authors could not identify any reported cases in which all three markers remained normal in the same patient, despite extensive literature search.

Thus, clinicians may encounter patients with AOSD in whom commonly used inflammatory markers remain normal, which can lead to delay in diagnosis and consequently result in prolonged and costlier treatment.

CONCLUSION(S)

AOSD can present with normal commonly used inflammatory markers such as CRP, ESR, and serum ferritin, which may delay accurate diagnosis and timely treatment. Although these markers are not included in the Yamaguchi diagnostic criteria, they assist clinicians in diagnosis, treatment monitoring, and detecting complications in AOSD. In such scenarios, as the markers are already within normal range, monitoring treatment response relies mainly on clinical features. Further large-scale studies are needed to assess AOSD cases with normal inflammatory markers and their correlation with clinical presentation.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 13, 2025
- Manual Googling: Sep 04, 2025
- iThenticate Software: Sep 06, 2025 (3%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jul 30, 2025**
Date of Peer Review: **Aug 22, 2025**
Date of Acceptance: **Sep 08, 2025**
Date of Publishing: **Feb 01, 2026**