

Adult-Onset Still's Disease - A Rare Cause of Pyrexia of Unknown Origin

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ABSTRACT

Adult onset still Disease is a multi-systemic auto inflammatory disorder manifesting as high fever spikes, evanescent rash and polyarthralgias. It has a bimodal age distribution with peak incidence in adults aged 15 to 25 and 36 to 45 years. Here we describe a case of a 35 year old male who presented in a tertiary care hospital with the complaints of fever, rash and joint pains, and negative rheumatoid factor and raised ESR and CRP levels. After excluding infectious and other autoimmune disorders, he was diagnosed as a case of Adult Onset Still Disease using the Yamaguchi and Fautrel Criteria. He showed a favorable response to steroid therapy and disease remission was attained. The patient was then started on a maintenance therapy of methotrexate. This case demonstrated the diagnostic challenges of AOSD and the importance of considering it as a differential while pyrexia of unknown origin (PUO) is encountered. While early diagnosis and treatment has a good prognosis.

Keywords:

Adult Onset Still Disease, Fever, Pyrexia of Unknown Origin

INTRODUCTION

Adult Onset Still's Disease (AOSD) is a systemic auto inflammatory disorder presenting with features of daily fever spikes, a salmon pink evanescent skin rash, polyarthralgia, neutrophilia, and hyperferritinemia and abnormal liver function tests.^{1,2} In 1986, Still's disease was first defined by George F. Still as a chronic disease of joints in children similar to rheumatoid arthritis in adults.³ However, in 1971, Bywaters explained an illness resembling Still's Disease in adult life.²

It is a multifactorial disease that gets initiated upon exposure to an environmental trigger and involves auto inflammatory reaction including increased expression of cytokines e.g. IL-1, IL-6, TNF-alpha, in a person having genetic susceptibility.^{4,5}

AOSD is one of the inflammatory causes of pyrexia of unknown origin.⁶ Pyrexia of unknown origin was first defined in 1961 as a persistent fever above 100°F that remains undiagnosed for at least 3 weeks, which includes 1 week of investigation in hospital.⁷

Valentin et al says there are three types of AOSD on the basis of the course of disease and its pattern of symptoms. The monophasic type has just one active disease period of systemic symptoms, and goes into remission within a year. The intermittent type has intermittent systemic symptoms and its remission period can vary from weeks to two years and the chronic type has persistent symptoms and requires continuous treatment.⁸ Complications that can arise in AOSD include macrophage activation syndrome, coagulation disorders, liver, cardiac or pulmonary complications and amyloid A amyloidosis.⁹

According to a retrospective study done in West France, its estimated prevalence was 0.16/100,000 cases and dichotomous age distribution, between 15-25 years and 36-45 years.¹⁰ and in a study performed in Pakistan, the incidence was 1.3 cases per year.¹¹

AOSD's presentation can resemble various infectious, autoimmune and neoplastic diseases, making its diagnosis difficult and therefore it is diagnosed on the basis of Yamaguchi Criteria, developed in 1992.¹²

Steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs), are used for the treatment of AOSD. Among all, steroids are used as first line agents.⁵

Here, we will present a case of a 35 years male who presented with fever of unknown origin and was diagnosed with AOSD, though had some variations from the typical presentation of AOSD like persistent rash and double quotidian fever pattern which served as a diagnostic challenge.

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CASE PRESENTATION

A 35-year-old male businessman presented in the emergency department of Sir Ganga Ram, a tertiary care hospital in Lahore, Pakistan, with the chief complaint of high-grade fever for 2 weeks. Fever was recorded up to 104°F with two daily spikes, one in the afternoon and the other at night, and was relieved by taking antipyretics. It was associated with chills and sore throat, which was most severe during the fever spikes, and the patient was unable to take anything orally. The fever was accompanied with pain, redness, and swelling of the left wrist, left knee, and the right ankle joint. The patient also developed a rash 1 week before presentation to the hospital. The rash was erythematous, nonpruritic, persistent, and not related to the fever spikes. There were no complaints of cough, sputum, shortness of breath, chest pain, abdominal pain, vomiting, diarrhea, or increased or painful urination.

On general physical examination, the patient was febrile and tachycardic. Salmon-pink maculopapular rash was present on the arms, legs, and trunk. No evidence of lymphadenopathy or hepatosplenomegaly was found. There were no other significant findings on systemic examination.

Laboratory investigations revealed raised total leukocyte count (TLC), ESR (60 mm/hour), and CRP. Liver function tests were deranged with ALT 66 U/L and AST 171 U/L, but normal bilirubin. Prothrombin time, partial thromboplastin time, and serum creatinine were in the normal ranges. Urine complete examination and chest X-ray were unremarkable.

Blood for culture and sensitivity tests was sent, and meanwhile the patient was started on IV antibiotics:

meropenem and azithromycin. Echocardiography was done, which showed no evidence of infective endocarditis. Blood culture and sensitivity report revealed growth of *Bacillus cereus* sensitive to vancomycin. Vancomycin was added to the antibiotic regime. Despite adequate antibiotic coverage, the patient's fever continued to spike in the following days, and his clinical condition did not improve. It was thought that culture growth might have been due to contamination, as this organism is not usually known to cause disease in immunocompetent individuals.

Subsequently, autoimmune and autoinflammatory pathologies were considered, and workup started. Anti-Nuclear Antibody (ANA) by immunofluorescence assay, Extractable Nuclear Antigen (ENA), Rheumatoid Arthritis (RA) factor, and anti-cyclic Citrullinated Peptide (anti-CCP) were found to be normal.

However, serum ferritin was reported to be very high, with a value of 27,919 ng/ml. Adult-onset Still's disease was diagnosed as the patient fulfilled several components of the Yamaguchi and Fautrel criteria. To rule out the possibility of complications such as macrophage activation syndrome, fibrinogen and serum triglyceride levels were checked, which were within normal ranges.

The patient was started on IV methylprednisolone 500 mg for 3 days. Fever settled on the day of initiation of steroid therapy. After completion of pulse steroids, he was switched to 40 mg per day oral prednisolone with the plan to initiate methotrexate after normalization of liver function tests. The patient responded well to treatment and is currently on methotrexate 20 mg/week and prednisone 10 mg, with the aim to further taper steroids.



Figure 1: Salmon-pink maculopapular rash seen on the forearms of the patient.

Table1: Trend of total leukocyte count (TLC) and C Reactive Protein (CRP) is shown below

	First admission day	Second admission day	Third admission day	Fourth admission day	Fifth admission day	Seventh admission day
TLC (mg/dl)	14.2	15.8	15.5	19.5	25.89	30.48
CRP (mg/L)	181.33		176.78	179.88		179.60

DISCUSSION

In Low to Middle Income Countries (LMIC) such as Pakistan, infectious diseases are the leading cause of PUO¹³. This might result in inflammatory disorders not being taken into account when dealing with patients presenting with PUO. In spite of its rarity and the lack of specific signs and symptoms, AOSD should be considered after excluding infections and malignancy. The Yamaguchi and Fautrel criteria are universally accepted as the best available guides for establishing its diagnosis^{12,14}. Yamaguchi Criteria¹²: ≥ 5 criteria must be met, including ≥ 2 major. All of the exclusion criteria must be ruled out. Major criteria include fever $\geq 39^{\circ}\text{C}$ for 1 week, arthralgia/ arthritis for 2 weeks, evanescent rash, leukocytosis $\geq 10,000/\text{mm}^3$ and neutrophil $\geq 80\%$. Minor criteria include sore throat, lymphadenopathy, hepatosplenomegaly, liver dysfunction on examination and negative antinuclear antibody. Infection, malignancy and any other rheumatic disease should be excluded. **Fautrel Criteria**¹⁴: ≥ 4 major criteria or 3 major and 2 minor criteria are required for diagnosis of AOSD Major criteria include spiking fever $\geq 39^{\circ}\text{C}$, arthralgia, transient erythema, pharyngitis, polymorphonuclear white blood cells $\geq 80\%$ and glycosylated ferritin $\leq 20\%$. Minor criteria include maculopapular rash and leukocytes $>10,000/\text{mm}^3$. 3 major and 2 minor components of the Yamaguchi criteria were fulfilled in this patient: fever $\geq 39^{\circ}\text{C}$ for 1 week, arthralgia/ arthritis for 2 weeks, leukocytosis $>10,000/\text{mm}^3$, sore throat and negative antinuclear antibody. The patient also met 3 major and both minor components of the Fautrel criteria: spiking fever $\geq 39^{\circ}\text{C}$, arthralgia, pharyngitis, maculopapular rash and leukocytes $>10,000/\text{mm}^3$.

However, there were a few notable distinctions from the usual presentation of the disease. Fever was double quotidian instead of the more common quotidian pattern. Moreover, the rash in this patient was not the typical evanescent kind¹⁵. It persisted regardless of the patient's febrile state and only resolved after initiation of intravenous steroid therapy.

Many similar cases have been reported where patients presenting with pyrexia of unknown origin were eventually diagnosed with AOSD. For example, Shad et al (2022) reported a 12 year old girl presenting with high grade fever of two weeks duration, arthralgias and the typical maculopapular evanescent rash associated with the disease. However, as compared to our case, this case was documented in a much younger age group and the patient met additional minor criteria of the disease such as cervical lymphadenopathy and hepatosplenomegaly.¹⁶ Agarwal et al (2022) also reported a similar presentation of the disease in a 26 year old woman. Unlike our case,

their patient developed macrophage activation syndrome with multi organ failure and remained unresponsive to intravenous steroid therapy, eventually succumbing to disease related complications.¹⁷ These cases highlight the differences in age distribution and the impact that prompt diagnosis may have on treatment responsiveness of the disease.

Current treatment practices for AOSD include the use of NSAIDs and DMARDs for early stage, uncomplicated disease, and high dose steroids such as prednisolone to achieve symptom control and remission. Various biological agents such as tocilizumab and anakinra have gained traction in recent years due to their effectiveness both as adjuncts to help taper steroid therapy and prevent disease relapse, and as useful modalities in severe, refractory disease.¹⁸ Unfortunately, their use is limited largely on account of administrative difficulties, strong immunosuppressive effects, need for regular follow up, and in the case of LMIC, the sheer costs.

Once ascertained that this patient was likely suffering from AOSD, he was promptly started on high dose IV methylprednisolone. He responded exceptionally well and clinical condition improved dramatically within hours. Methotrexate was added to the treatment regime and in due time steroid tapering will be attempted. Tocilizumab was reserved as a second option in case of unresponsiveness to steroids or disease relapse.

CONCLUSION

This particular case highlights the difficulty in diagnosing rare disorders such as AOSD in a LMIC setting, where infectious diseases are largely prevalent. For patients presenting with PUO, serum ferritin level can serve as an inexpensive yet effective tool, aiding in the early detection of AOSD. Prompt diagnosis and swift intervention mean patients are more likely to achieve remission, without the development of complications. It is also important to note that substantial variation exists in the presentation of AOSD as evidenced by the persistent rash and double quotidian fever pattern in this particular patient.

Author Contributions

Dr. Shamas U Din: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval.

Dr. Fizza Khalid: Conception and design, analysis and interpretation of data.

Dr. Auj Sohail: Analysis and interpretation of data, drafting the article.

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