

## A rare clinical presentation: Adult-onset Still's disease

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### Abstract

Adult-onset Still's disease (AOSD) is a rare, idiopathic, inflammatory disorder of unknown etiology and pathogenesis that presents in 5 to 10% of patients as fever of unknown origin (FUO) exclusion characterized by generalized migratory joint ache, blanchable rash, fever and other systemic manifestations. We report an interesting case of a 23 year old Nepalese lady from Okhaldunga who presented with one-month duration of FUO along with sore throat, fever, vomiting, generalized joint ache, erythematous blanchable rash, headache and visual impairment. On examination there was hepatomegaly and investigations showed raised liver enzymes, serum ferritin and fibrinogen. After extensive workup, potential differential diagnoses were ruled out. She was diagnosed to have Adult-onset Still's disease based on Yamaguchi criteria after exclusion of other potential differentials. The patient partially responded to prednisolone and later methotrexate was prescribed which improved her symptoms. The case history, incidence, pathogenesis, clinical manifestations, differential diagnoses, diagnostic workup, treatment modalities, and prognosis of AOSD are discussed in this case report.

**Key words:** Adult-onset still's disease; Blanchable rash; Fever; Methotrexate; Migratory arthritis.

### INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown origin. Recent studies suggest four hypothesis of AOSD origin infectious, autoimmune, lymphohistiocytic and hyperferritinemic respectively<sup>1</sup>. Several viruses such as rubella, echovirus 7, mumps, cytomegalovirus (CMV), and others, as well as bacterial pathogens including *Yersinia enterocolitica*, *Chlamydia pneumoniae*,

*Brucella abortus*, and *Borrelia burgdorferi*, have been so far described in various literature<sup>2-5</sup>. Several small case studies have also shown association with various Human Leukocyte Antigen (HLA) with conflicting results suggesting autoimmune origin<sup>6</sup>. The prevalence of AOSD is estimated to be one per 100,000 people<sup>7</sup>. The disease mainly affects young adults and has a bimodal age distribution at 15-25 and 36-46 years of age<sup>8</sup>. In 1896, the first case of an adult patient with signs and symptoms of AOSD was published. Subsequently, Bywaters described 14 adults with similar presentations and the term AOSD was used in 1971<sup>9</sup>. We discuss atypical presentation of the disease here. There has not been any extensive case study conducted in our country in this disease. Since it is rare, medical staff often face challenge in diagnosis and procedures.

### CASE REPORT

A 23 year old female presented with complaints of high grade fever with chills, rigor for three days and vomiting of gastric content for the same duration. Fever subsided with a stat dose of Paracetamol. On the same day four hours later she developed severe migratory arthralgia which started initially at the left elbow and was generalized later. On examination, temperature was measured to be 39.4 degrees C with chills and rigor. There

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were multiple blanchable, pruritic and erythematous rash over chest, back and arm.

Laboratory examination showed anemia with hemoglobin 7.6mg/dl. Temperature of >39.4 degree C with chills and rigor was present. Complete blood count showed leukocytosis with lymphocytic predominance, platelet count of 1,10,000/mm<sup>3</sup> and raised Erythrocyte Sedimentation Rate (ESR) of 48-60mm/hr. Serum ferritin was raised to 23,560mcg/l and serum fibrinogen of 2.2. Aspartate Transaminase /Alanine Transaminase were raised. Viral screening, ASO Titre, Anti-nuclear Antibody, Rheumatoid factor, Montoux test, blood culture and sensitivity were negative. Peripheral blood film showed only reactive lymphocytes. The titre of *S. Mycoplasma* was 1:320-1:640 and *S. Chlamydia psittaci* was positive. Bone marrow aspiration test with eosinophilia 10% (0.8), normal echocardiogram and Contrast Enhanced Computed Tomography (CECT) abdomen and pelvis were normal. Skin biopsy showed perivascular infiltrates with neutrophilic predominance.

Patient was then started on intravenous (IV) Augmentin for two days which was then upgraded to IV Ceftriaxone and Tablet Doxycycline. Ceftriaxone was then changed to Cefepime which was continued for five days despite which fever did not subside. Patient was put on IV Meropenem and IV Dexamethasone 4mg thrice a day (TDS) after diagnosis of HLA + AOSD using Yamaguchi criteria was made<sup>25</sup>. Patient was discharged after 15 days of admission on NSAIDs and steroid which was tapered gradually.

Three days after being discharged, she developed headache followed by anorexia and anterograde amnesia but she did not visit the hospital. Five days later, she presented with excruciating headache and intermittent fever. Patient was started again on IV Prednisolone, IV Ceftriaxone, Tablet Azithromycin and antipyretic but fever did not subside. Patient denied Lumbar puncture and then all antibiotics were stopped. The patient was then started on Methotrexate, Prednisolone with Aspirin and antipyretic as per need (SOS). Patients' condition improved and was then discharged on steroid which was gradually tapered.

## DISCUSSION

AOSD was first described by Eric Bywaters in 1971<sup>9</sup>. The exact etiology is unclear but there are recent hypotheses of genetic, environmental and infectious etiology. There is a correlation between several cytokines in the pathogenesis of AOSD, including Tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6) and Interleukin-18 (IL-

18). The levels of these cytokines are highly elevated in active AOSD<sup>10</sup>.

Patients with AOSD typically present with fever, rash, arthritis and sore throat. Fever is usually more than 39 degree centigrade and predominant over morning and evening. Rash is salmon colored, evanescent, blanchable and pruritic occasionally dominant over trunk and extremities. Arthritis is one of the major clinical manifestations of AOSD. Its severity increases with the onset of a spike of fever. Major joints involved are wrist, knee, elbow and ankle. It can result in destruction of joints, mostly carpal joints. Sore throat is also a major clinical entity that can result in odynophagia in the patient. Other features of lymphadenopathy, hepatosplenomegaly, aseptic meningitis, pericarditis, pleuritis and peritonitis are also not uncommon<sup>11-22</sup>.

Laboratory investigation shows marked elevation of acute phase reactant (Erythrocyte Sedimentation Rate, serum ferritin, C - reactive protein) and neutrophil leukocytosis. Disproportionate elevated serum ferritin is present in 70% of cases<sup>16</sup>. Elevated liver enzymes are present in a quarter of the population<sup>23</sup>. Rheumatoid factor and antinuclear antibody are generally negative as in our patient<sup>24</sup>.

The Yamaguchi criteria (1992), is the most widely used criteria to diagnose AOSD with a 93.5% sensitivity<sup>25</sup>. In this criteria, there are four major and four minor criterias with three exclusion criterias. The 4 major criterias include: arthralgia more than two weeks, fever more than 39° degree centigrade for more than one week, typical rash and leukocytosis (more than 10,000/mm<sup>3</sup> including more than 80% granulocytes). The four minor criteria include: sore throat, lymphadenopathy or splenomegaly, liver dysfunction, negative (Rheumatoid Factor) RF and (Antinuclear Antibody) ANA. Five or more criteria must be met in order to make a diagnosis of AOSD, including two or more major criteria, after excluding infections, malignancies or rheumatic diseases. The patient in this report fulfilled four major and three minor criteria.

In a multicenter survey of Japanese patients(1990), out of 146 cases from 32 different institutes, 90 patients presented with high fever, polyarthralgia, rash, increased erythrocyte sedimentation rate, negative for autoantibodies (ANA, RF, anti CCP), leukocytosis, liver dysfunction, and hyperferritinemia same as the case we report<sup>12</sup>.

Abubake et al. showed that in 20 cases, variable presentation of symptoms like -fever (100%), arthralgia (65%), skin rash (60%), arthritis (40%), hepatomegaly

(40%), splenomegaly (35%) and lymphadenopathy (15%) were present. There was no any typical salmon colored skin rash like in our case<sup>32</sup>. Only 15% were ANA positive and 10% were Rheumatoid factor positive but our case had both test negative. Serum ferritin was higher in 17 out of 20 patients in his study ranging from 300 to >10,000. In our case serum ferritin is 23,560 mcg/l<sup>32</sup>.

Study showed that elevated serum ferritin (>10,000 mcg/l), hepatosplenomegaly, positive ANA and RF were associated with poor prognosis factor which was related to relapse and one case out of 20 had died due to complication<sup>32</sup>.

Yagamuchi (1987) review of 228 cases showed frequent recurrence; one third among the cases developed deformed arthritis with ankylosis and six deaths were recorded.

Non-Steroidal Anti Inflammatory Drugs (NSAIDs) or Aspirin is the recommended first line therapy but with low response. Then, Prednisolone should be added for better effect. If the patient still does not improve clinically, Disease Modifying Anti-Rheumatic Drugs (DMARDs) like Methotrexate will show good response. But Methotrexate should be given for six months for therapeutic effect. If improvement is still not seen, biological agents should be considered like etanercept<sup>26-29</sup>.

Three different patterns have been described in AOSD and the prognosis is variable<sup>30</sup>. The first category of patients tend to have monocyclic or self-limited patterns with complete remission within a year. The second group has intermittent or polycyclic patterns with recurrence of systemic and articular flares separated by periods of remission as seen in our patient. The final group shows chronic joint problems and are prone to joint destruction<sup>31</sup>.

## CONCLUSION

AOSD is a rare entity of unknown etiology and pathogenesis. It should be kept in consideration with complaints of fever, rash, arthritis and sore throat after excluding malignancy, infections and rheumatic diseases. If case is timely diagnosed, we can focus on manifestations with poor prognosis and can prevent from worse outcome as much as possible but if undiagnosed, the patient has to undergo ample interventions and medical therapy rendering risk of drug resistance, prolonged hospital stay, financial burden in every relapse and can ultimately lead to deformity or iatrogenic mishaps.

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