

Adult Onset Still's Disease (AOSD) – A Case Report

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We report here, possibly the first documented case of Adult Onset Still's Disease (AOSD) in Bahrain. The patient presented to Salmaniya Medical Complex (SMC) with a picture of acute renal colic followed shortly by triad of arthritis, fever and rash, which was preceded by history of sore throat for one month. Non invasive investigation and evaluation of pyrexia of unknown origin was carried out to this patient and the diagnosis of AOSD was considered after documentation of triad of fever, rash and arthritis and observation of the patient over a period of six weeks according to Yamaguchi criteria. The patient responded well to combined NSAID and steroid. The case history, incidence, pathogenesis, treatment modalities and prognosis of AOSD are discussed.

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THE CASE.

The patient is a 23 years old Bahraini male, who was healthy apart from Glucose-6-phosphate dehydrogenase deficiency, non-smoker non-alcoholic, presented to SMC in the second week of April 2001 with fever and severe left renal colic for one week duration and admitted under surgical care. Intravenous Pyelography (IVP) and renal ultrasound were normal. Following one week of continuous fever he developed generalized itching, macular rash mainly in upper thighs and painful synovitis affecting mainly left elbow and hands for which rheumatology consultation was obtained.

The patient's problem appears to have started 6 weeks prior to admission when he was in Haj with continuous sore throat and was not responding to several oral antibiotics. This was followed by triad of fever mainly at night with evanescent macular rashes especially in upper thighs and back, with polyarthritis involving tempro-mandibular joint (TMJ), wrist, proximal interphalangeal joints (PIP), metacarpophalangeal joints (MCP), knees and ankles of three weeks duration and progressive loss of five Kg of weight over 3 months duration. There were no early morning stiffness, ocular symptoms, orogenital ulcers, urinary symptoms, photophobia, contact to infected person or major systemic symptoms. During the third week of stay in hospital he developed pleuropericarditic pain for two days, which subsided with steroid therapy.

Examination revealed well built, oriented young male with heliotropes like rash around the eyes and macular rashes over both thighs and lower back and there was no rash over his finger knuckles. The patient was febrile 39.5°C with regular heart rate 100/min, blood pressure of 130/70 mmHg and normal jugular venous pressure. He had acute synovitis of ankles, wrists and PIP joints, mainly of ring fingers with weak hand grip bilaterally, but full range of movements of all locomotor system and no proximal or distal muscular weakness. Deep tendon reflexes were normal.

Examination of chest, abdomen, central and peripheral nervous systems were unremarkable and so was his ears, nose and throat examination.

Investigations for his pyrexia revealed sterile throat swab, blood cultures, urine cultures, stool cultures. Sputum culture was negative for acid fast bacilli in three samples.

Haematological investigations revealed normocytic normochromic anemia with hemoglobin of 10.9g/dl, platelets $182 \times 10^9/L$ and total leukocytic count of $4.1 \times 10^9/L$ with normal differential, high Erythrocytes sedimentation rate of 58mm/1st hour and abnormal liver function with mild hypoalbuminaemia 22mg/L (N-R=38-50) and elevated liver enzymes, alkaline phosphates 144u/L (N-R=50-136), ALT 158u/L (N-R=30-65), and GGT476u/L (N-R=5-85)- with normal bilirubin level and slightly high CPK339u/L (N-R=21-323), normal aldolase and high LDL 919u/L (N-R=100-190).

The electrolytes, renal parameters, sugar profile, serum calcium, serum phosphate, serum magnesium, coagulation profile, direct and indirect comb's tests and thyroid function test were all normal. His initial urine microscopy showed microscopic haematuria, but was normal on repeats.

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The thick and thin films for malarial parasites, serological tests for typhoid, toxoplasma and brucella were all negative.

Other serological studies revealed marked acute phase reactant with high CRP13.6 (NR=0-0.5mg/dl) and hyperferritinemia, negative Anti Nuclear Antibody (ANA), anti DNA, ASO titer, sickling test and non-reactive VDRL, normal C3, C4 levels, and negative antibodies for SS-A, Ribo Nucleo Protein Antibody (RNP Ab), Scl-70.

Arterial blood gases (ABG), ECG, Echocardiogram and radiological assessment (including CXR, hand X-ray, sinus X-ray, I.V.P, and abdominal ultrasound) all were normal. Because of more than eight weeks illness, three of whom were in hospital with continuous quotidian like fever of more than 39°C, sore throat, arthritis and macular evanescent rashes, marked acute phase reactant- high CRP, ESR and ferritin-liver dysfunction, negative ANA and RA latex and negative non-invasive workup for pyrexia of unknown origin (PUO) with total duration of eight weeks, definite AOSD diagnosis was made according to Yamaguachi criteria and he was started on prednisolone 45mg daily and NSAID (Diclofenac sodium 100mg daily) after which he became afebrile for the first time in eight weeks after onset of illness.

The patient showed considerable improvement and was discharged home after one week on prednisolone 45mg daily with tapering dose of 5mg weekly, Diclofenac sodium and ranitidine 150mg twice daily.

Six weeks later the patient had a relapse in the form of bilateral wrist synovitis, this was controlled by adding oral methotrexate 7.5mg and folic acid 5mg weekly. He was seen in outpatient clinic regularly. In the last visit on September 2001 he was totally afebrile, asymptomatic, clinically well with normal ESR, LDH, liver function test, and

on same dose of methotrexate, folic acid and prednisolone 5mg alternate day. He is back on normal work duties.

DISCUSSION

Adult Onset Still Disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology and pathogenesis that typically affects young adults aged between 16-35 years. It includes three variants of arthritis found in pediatric age group in the form of rheumatoid arthritis (RA), chronic fibrous rheumatism (Jaccoud's arthropathy) and systemic onset type (Still's disease) described by George Friderick Still (1897). It has been recognized with increasing frequency since the first description by Bywaters in 1971¹.

AOSD is a rare disease affecting all races. The demographic study revealed a higher prevalence of female patients and a relatively younger onset of male patients compared with female. The reported prevalence is one per 100.000 adults aged between 16 and 35 years².

The etiology of AOSD remains unknown, although some authors think that infective agents, especially viruses can be the trigger of the illness in susceptible patients³. The viruses most commonly implicated in AOSD include rubella, parainfluenza, Epstein Barr virus, Echovirus and parvovirus B19. A viral triggering mechanism is most often identified by raised antiviral antibodies¹.

There is strong association between cytokine and chronic articular disease in AOSD. Tumor necrosis factor (TNF), interleukin(IL)-18 were increased in both types of AOSD, even in remission. Soluble receptors, IL-4, IL-18 level and IL-8 were correlated with disease activity¹³.

Stressful life events in the year preceding onset are significantly associated with increased risk for AOSD and there are no significant associations of AOSD with smoking, alcohol consumption, individual toxic substances, vaccination, blood transfusion, trauma or surgery, pregnancy or oral contraceptive use⁴.

Patient with AOSD typically present with high spiking fever, which is usually accompanied by an evanescent pink or salmon-colored macular rash on the trunk and proximal extremities⁵. Arthralgia and polyarthritis appear later in the disease course and may be intermittent in early stages. Sore throat is common at onset, but cultures for group A streptococci are negative.

The major clinical manifestations consisted of fever, joints symptoms and rash, which were seen in almost all of the patients. Most had high temperature 39°C or higher, which lasted one week longer before treatment. Apparent arthritides which lasted two weeks or longer, with three or more joints affected and also with normal findings on joint roentgenographs at the time of diagnosis, were seen in most of the patients. Typical rash was present in 87% of the definite cases, but another type of rash such as urticarial eruption and eczema was seen in a few cases¹².

Symmetrical or asymmetrical polyarthritis is found in more than 90% of patients during the first 6 months involving both large and small articulation (knees, wrists, ankles, elbows, shoulders, PIPs, DIPs, TMJ and cervical spine). Initially synovitis may be fleeting or migratory, however the chronicity of synovitis is rare. These patients who had a chronic articular pattern or a polyarticular onset and course were at higher risk for develop disabling arthritis¹⁷.

Other features may include pericarditis, pleuritis, splenomegaly and lymphadenopathy⁵. Recent reviews of AOSD have emphasized the chronicity of this disease as well as highlighting involvement of major organ systems. Central and peripheral nervous system involvement is rare which include brain stem hemorrhage, seizures with fatal epilepticus, ophthalmoplegia and encephalopathy were reported¹. Although thrombotic thrombocytopenic purpura (TTP) has been associated with autoimmune disease, usually with systemic lupus erythematosus or various form of vasculitis, it has rarely been observed in patients with AOSD¹⁸. Patients with AOSD can develop multi-organ failure, which may be a manifestation of disease itself or secondary to gold therapy².

Laboratory studies show only non-specific abnormalities including anemia, leukocytosis with predominance of neutrophils, marked ESR elevation and thrombocytosis in most patients. Serum ferritin behaves as an acute phase reactant and is increased in many inflammatory and infectious illnesses, but for unexplained reasons it is disproportionately elevated in patient with AOSD⁶⁻¹⁰. However an increased serum ferritin level is a nonspecific finding and should not be regarded as a diagnostic test⁽⁶⁻¹⁴⁾. 80% or more of the patients present with high ESR, negative ANA, negative RF, leukocytosis, granulocytosis and liver dysfunction¹².

Making a diagnosis is difficult in the early stages of the disease, but is facilitated by ruling out infectious illnesses, recognizing the typical rash, and noting the development of chronic polyarthritis which resembles R.A. Diagnosis of AOSD should be considered in the course of evaluating patients with triad of fever, rash, arthritis, documentation of fever pattern and observation of patient over a minimum of at least 6-8 weeks prior to the possible diagnosis of AOSD¹⁵.

The Yamaguchi criteria 1992 (specificity 92% and sensitivity 96%) is the most widely used criteria to diagnose AOSD¹⁵.

<p>Major criteria: fever of 39°c or higher, lasting 1 week or longer arthralgia lasting 2 weeks or longer typical rash leukocytosis (10,000/mm³ or greater) including 80% more of granulocytes</p> <p>Minor criteria: Sore throat Lymphadenopathy and/or splenomegaly Liver dysfunction Negative RF and negative ANA</p> <p>Exclusions: I. Infections (especially, sepsis and infectious Mononucleosis) II. Malignancies (especially, malignant lymphoma) III. Rheumatic diseases (especially, polyarteritis Nodosa and rheumatoid vasculitis with Extraarticular features)</p>
<p>Classification of adult still's disease requires 5 or more criteria including 2 or more major criteria. Any disease listed under " Exclusions" should be excluded.</p>

Therapy of AOSD is directed to control inflammatory symptoms and signs without exposing the patient to unacceptable toxicity. About 25% of patients respond to

NSAIDs and the remainder requires steroid therapy to suppress the acute systemic illness⁵. Systemic disease activity will require aggressive anti-inflammatory therapy with NSAIDs, steroid, methotrexate or hydroxychloroquine and will not respond to other conventional DMARD (gold and penicillin). Methotrexate and corticosteroids in combination may be indicated for the treatment of AOSD when polymyositis and erosive arthritis occur⁷. Methotrexate can be used to control the acute symptoms and it is suggested that at least 6 months of therapy should be considered to allow adequate time to assess therapeutic effect with close monitoring of full blood count and liver function test¹⁶. Infliximab may be effective in treatment of relapse of AOSD refractory to conventional therapy and requiring continuous high dose corticosteroid medication⁹.

AOSD has a highly variable course with some patients entering remission, others having intermittent exacerbations, others developing a chronic persistent disorder. Although the disease course is relatively benign, some recent studies have concluded that the outcome of AOSD is unfavorable⁸. Those patients who had a chronic articular pattern or a polyarticular onset and course were at high risk to develop disabling arthritis¹⁷.

CONCLUSION

AOSD is a rare systemic inflammatory disorder of unknown aetiology and pathogenesis. It should be considered in the course of evaluating patients with triad of fever, rash and arthritis with non-invasive workup for PUO, along with documentation of fever pattern and observation of patient over a minimum of at least 6-8 weeks.

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