Adult Onset Stills Disease: Rare But Not Uncommon

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Abstract: Adult Onset Stills Disease is a rare clinical entity without any known etiology which characteristically presents with fever, rash, arthritis, along with other systemic manifestations. We present the case of a 26 years old male presented with multiple joint pain, high grade fever and rash since 2months. The patient was extensively evaluated for pyrexia of unknown origin and treated with weeks of intravenous antibiotics without any benefit. Applying Yamaguchi's criteria, he was diagnosed to have Adult Onset Stills disease. Patient responded very well to systemic steroids and fever and joint symptoms resolved completely. He required addition of methotrexate as steroid sparing agent as attempts of tapering prednisolone lead to recurrence of symptoms. AOSD remains a very rare but treatable cause of fever and joint pain and high index of suspicion is required for diagnosis. [Shah A Natl J Integr Res Med, 2020; 11(5):75-78]

Key Words: Adult Onset Stills Disease, Hyperferritinemia, Yamaguchi Criteria, Methotrexate, Pyrexia of unknown origin (PUO)

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Introduction: Adults Onset Stills Disease[1] refers to a rare systemic auto inflammatory condition with infection, environmental and genetic predispositions are being considered as few etiologies however none of them is confirmed. Still's Disease is named after English physician Sir George Frederic Still (1861-1941). The Adult onset variant was characterized by E.G. Bywaters in 1971. In 2009, Owlia et al. from Iran reviewed more than 1,000 PubMed titles and reported that the crude prevalence of AOSD was 1.5 cases in 100,000–1,000,000[2]. Young adults are affected with female preponderance and bimodal age distribution 15-25 and 36-46 years of age is seen; can also be seen in elderly individuals[3]. The presenting complaints usually are: high spiking fever, evanescent rash, arthritis, leukocytosis, and raised liver Enzymes. The patient here has typical presentation of AOSD.

Case Report: A 26years old male presented with multiple joint pain involving bilateral limb large joints along with evening spiking high grade fever, an evanescent rash aggravating during fever spike since 2 months and sore throat since 1 month. The patient needed hospitalization for his symptoms and was treated with IV antibiotics and multiple anti-inflammatory drugs without any benefit. The joint pain and swelling affected shoulder, elbow, wrist, knee and ankle joint causing difficulty in ambulation. As per patient he had similar episode around 2 yrs back for 1 month which got resolved on anti-inflammatory and analgesic medications.

On Examination patient was well built, febrile with temperature of 102^0 F, with a pulse rate of 116/min and blood pressure of 126/78mmHg. There was reddish non blanching, non pruritic, non palpable maculopapular rash over the back, arm and thigh. Throat and posterior pharyngeal wall were mildly congested with swollen tonsillar pillars. There were multiple subcentimetric cervical and inguinal lymph nodes with free mobility and normal consistency. On Musculoskeletal examination, red, swollen, tender and warm joints, limiting active and passive range of movement of patient were found. On Systemic Examination, 1 finger breadth hepatomegaly was noted and rest other systems were normal.

Haematological investigations revealed leukocytosis ($16500/mm^3$), with normocytic normochromic anemia (Hb 10.3gm/dl), with elevated Erythrocyte Sedimentation Rate (ESR) (90) and C-Reactive Protein (CRP) (96mg/L), elevated Liver enzymes [SGPT (127 IU/ml); SGOT (54 IU/ml) and ALP (203 IU/ml)]. Serology for Dengue NS-1, IgM; Chikungunya IgM; Anti Streptolysin O (ASO) titre (84.98 IU/ml) were negative. Blood Culture sent twice, Urine Culture and Throat Swab were negative.

Rheumatoid Factor (RF), Anti Cyclic Citrullinated peptide (Anti-CCP) were negative. Antinuclear Antibody (ANA) by IF showed 1:100 with coarse speckled pattern however, ANA profile by Immunoblot was negative. Chest Xray was normal and Xrays of hand and other joints were normal. USG abdomen showed mild hepatomegaly. Contrast enhanced Commuted Tomography of abdomen plus pelvis and Thorax showed hepatomegaly with fatty infiltration. 2D

ECHO did not reveal infective endocarditis. The diagnosis of Adult Onset Still's disease is usually a diagnosis of exclusion. Infectious diseases like CMV virus, Hep B and HepC, coxsackie parvovirus, Infective endocarditis, Lyme's disease and tuberculosis should be excluded; malignancies like lymphoma, leukemia should be excluded, Granulomatous and Connective tissue disorders should be excluded, after exclusion of all such diseases Adult onset stills can be diagnosed using Yamaguchi criteriai[4].

Based on his clinical features and laboratory investigations, he was diagnosed to be having AOSD using Yamaguchi Criteria (sensitivity 92%, and specificity 96%). Patient showed improvement on systemic steroids and methotrexate 15 mg once a week was added as steroid sparing drug. However patient discontinued all medications after a span of 3 months and remained asymptomatic.

Discussion: AOSD is a rare systemic auto inflammatory condition with unclear etiologies like Genetic, Environmental, infectious could be possible. In AOSD, cellular immunity involving innate immunity and adaptive immunity and also including various cytokines and chemokines play role. IL-18; IL-6; IL-2 and others like Tumour necrosis factor alpha; Tumour growth factor beta etc are playing central role in pathogenesis of AOSD[5,6,7,8].

Typically patient presents with high grade fever, arthralgias, sore throat and rash, arthralgia being the most common among them[9]. The fever is usually a high spiking quotidian fever (>1010F) with evening spikes. The fever is in association with other constitutional symptoms like cold or cough but can present as Pyrexia of unknown origin(PUO) alone[10]. The characteristic rash of AOSD is a transient, nonpruritic, salmon coloured, macular, or maculopapular lesion often observed during febrile episodes[11] the most common location usually involves trunk and proximal extremities and sometimes it shows koebner's phenomenon[12] and dermographism[13].

Other features includes lymphadenopathy[14], hepatospleenomegaly, pericarditis, pleural effusion and rarely CNS involvement like aseptic meningitis or sensorineural hearing loss[15]. Another life threatening condition that develops in the patients of Adult Onset Still's Disease is Macrophage Activation Syndrome (MAS) and reactive hemophagoytic system (RHS)[16].

Laboratory studies shows leukocytosis(usually >10,000/cu.mm with neutrophilic predominance) with raised inflammatory markers (ESR,CRP), elevated ferritin[17] which is a characteristic of Adult Onset Still's Disease and around 70% of the patients have it, which is due to increased cytokine secretion by reticuloendothelial system/Hepatic damage. Among various available cytoforms glycosylated ferritin is a form which is usually decreased in patient of AOSD. It has been shown that a combination of glycosylated ferritin fraction <20% and ferritin level above the upper limit of the normal range improved the diagnostic sensitivity and specificity to 70.5% and 83% respectively as compared to elevated ferritin levels alone[18]. Other laboratory findings include normocytic normochromic anaemia, elevated levels of hepatic transaminases[19]. Antinuclear antibody profile and RA factor are usually negative[14]. Bone Marrow aspiration and biopsy which show hemophagocytosis help in establishing the diagnosis of MAS[20]. Synovial fluid analysis reveals inflammatory type picture with neutrophilic predominance[21]. The radiographic evidence are usually helpful in the late or chronic phase of the disease where the erosions and joint space narrowing manifests, carpometacarpals joints are more commonly involved comparedto trasometatarsal joints[22].

Course Of Disease[23]: The clinical course of Stills disease is divided into 3 patterns:

- Monophasic pattern has fever, rash, serositis and hepatospleenomegaly, and lasts for weeks to months and resolves in less than a year.
- Intermittent pattern has disease flares with complete remissions between episodes lasting from weeks upto one or two years.
- Chronic pattern has disease in active form in which articular symptoms usually predominates.

Treatment Includes NSAIDS, Steroids and DMARDS such as methotrexate, cyclosporine, azathioprine have been used to control acute symptoms and suggested that 6 months of therapy should be given to allow ample time for assessment of therapeutic effect. Patients should be started with ample dose of either oral or

injectable steroids and then tapered over adequate time with addition of a steroid sparing agent as DMARDS. For resistanant Patients biologic agents like anti-TNF alpha (infliximab,etanercept and adalimumab)[24,25,26,27,28], IL-1 antagonists (anakinra, canakinumab, and rilonacept) and IL-6 antagonists(Tocilizumab) are used. Such patients are termed as refractory AOSDS[29,30,31,32]. IL-1 blockade is considered a mainstay in the treatment for refractory AOSD. However, in further resistant cases, IL-6 antagonists like Tocilizumab is used, it has a very good steroid sparing effect with good tolerance profile and less frequent dosing at the frequency of intravenous or subcutaneous injection every 1-2 weeks[33,34]. Plasma exchange[35] and intravenous immunoglobulins are other available but controversial treatment options.

Conclusion: AOSD is a rare disease with etiology and pathogenesis. It should be considered in patient presenting with rash, arthritis and fever excluding other differentials like Malignancy, infection, Rheumatic disease. And Proper follow up of the patients should be ensured and it should always be kept in mind while evaluating any patient of pyrexia of unknown origin.

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Conflict of interest: None
Funding: None
Cite this Article as: Shah A, Adult Onset Stills Disease: Rare But Not Uncommon. Natl J Integr Res Med 2020; Vol.11(5): 75-78