Adult onset still’s disease (AOSD) : A case report
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Abstract
A 30 years old male was admitted in BIRDEM hospital with fever, sore throat, cervical lymphadenopathy. Investigations failed to establish a microbial etiology of fever and empirical treatment with numerous antibiotic failed to resolve fever. Patient became a typical case of PUO. Later, the development of evanescent skin rash and polyarthritis pointed to a possible rheumatological diagnosis. With the help of very high serum level of ferritin and fulfillment of diagnostic criteria- a final diagnosis of Adult onset Still's disease was made. Patient was treated with combinations of NSAID and DMARD leading to remission. AOSD is one of the causes of PUO and early and aggressive treatment can herald possible fatal deformity and sufferings.

Introduction
Adult onset Still's disease is a recently recognized systemic inflammatory disorder of unknown etiology and pathogenesis. It is likely to be the continuum of systemic onset juvenile arthritis. It was initially described in 1897 by George F. Still, a pathologist. The characteristic features of this illness have subsequently been reported in adults, as detailed by Eric Bywaters in 1971. No etiopathogenesis has been acceptably proven for AOSD. An infectious etiology has been inferred based upon the prodromal sore throat, reflecting non specific cytokines mostly IL-5, IL-6, IL-18, TNF-α. Although the disease is a sero-negative chronic poly-arthritis, the initial presentation is almost always with fever and other non-specific manifestation. Most of the patients (about 75%) are between 16 -35 years age. Most striking manifestations are - quotidian fever, evanescent rash, prodromal sore throat, arthritis/arthritis, malaise, weight loss. Because arthritis is typically late onset, patient had already under gone numerous investigations and courses of antibiotics for presumed infections , till it became a case of PUO. 5-6% of patients being evaluated for PUO may be diagnosed eventually as Adult onset Still's disease. AOSD remains a clinical diagnosis of exclusion; with typical clinical features, laboratory abnormalities and absence of other explanations. Various diagnostic criteria have been proposed. Among them Yamaguchi criteria has the greatest sensitivity and specificity.

Case History
The 30 years old non diabetic, normotensive, non-smoker, married male developed fever, which was high grade with maximum temperature of 104°F, intermittent in nature, associated with chill and rigor, subsided by sweating. Fever occurred mostly at late night, persisted for 2-4 hours and then subsided. During fever patient felt extremely weak and tired. During that time patient was treated with oral antibiotics, initially Cephradine, then Azithromycin and Ciprofloxacin; keeping in mind differential diagnosis of pharyngitis and enteric fever. Patient had neutrophilic leucocytosis, high ESR. Blood C/S, urine C/S, throat swab C/S, ICT for Malaria, triple antigen all were negative. With antibiotics fever decreased but without complete remission. About 2 wks of fever, patient developed rash with high swinging temperature. The rash was pink colored,
maculo-papular, distributed on upper chest, back and upper limb. The rash was most noticeable at the height of temperature. The investigations revealed persistent neutrophilic leucocytosis, raised hepatic enzymes with normal bilirubin. All the microbiological tests were again negative. Chest X-ray, USG of whole abdomen was normal. At that moment, left cervical lymphnodes were palpable. They were 2 in number, firm, tender, discrete. A lymph node biopsy was done to exclude tuberculosis, it showed chronic non specific lymphadenitis. During that period patient was treated with I/V antibiotics-ceftriaxone, gentamycin, but there was no response. An echocardiogram was done to exclude infective endocarditis, revealed only minimal pericardial effusion. About one week after admission, patient developed arthralgia followed by arthritis involving multiple big joints, e.g. shoulder, hip, wrist, elbow. This pointed to a possible rheumatological diagnosis. Because of the combinations of high fever, arthritis, evanescent rash, sore throat and lymphadenopathy-Adult onset Still's disease was assumed to be a possible diagnosis. Serum RA, ANA, both were negative, CRP was positive and serum ferritin level was found to be significantly elevated. So with fulfillment of diagnostic criteria (yamaguchi criteria) and exclusion of other causes-a final diagnosis of Adult Onset Still's disease was made.

Patient was treated with NSAID. Aspirin was chosen and given in high dose - 2400 mg daily along with a proton pump inhibitor. After 3-4 wks after starting the treatment, most of the systemic features were improved with subsidence of fever, improvement of appetite & weakness. But the arthritis did not subside completely. Investigations showed persistent neutrophilic leucocytosis, high ESR, raised hepatic enzymes & serum ferritin level higher than before. So decision to start DMARD was taken. Hydroxy chloroquine was preferred over Methotrexate considering safety profile. 4 wks after starting Hydroxychloroquine 200 mg daily along with Aspirin, the patient had complete clinical & biochemical remission.

Discussion
This multisystem inflammatory disease has some common articular and non-articular manifestations together with typical laboratory findings. Most common clinical features of AOSD are - arthralgia (98-100%), fever > 39oc (83-100%), Myalgia (84 - 90 %), rash (87 - 90%), sore throat (50 - 92%).
Fever is an early feature, quotidian or diquotidian in pattern with rise of temperature in early morning/late afternoon. Patient with AOSD generally feel very ill while febrile & feel well when body temp is normal. This poses a dilemma for the physicians because hospital rounds usually do not occur during the times when the patient is febrile. Also here in this case the young male looked absolutely fine during morning rounds but the temperature chart showed high spikes at midnight associated with severe myalgia. So the patient received a number of antibiotics for presumed sepsis.

The rash of Still's disease is a salmon-pink colour evanescent rash, particularly on upper part of the body. It is often unappreciated unless specifically sought and may be seen only when the patient is febrile. The rash shows Koebner phenomenon and dermatographism. The patient also stated that he had similar rash for a few days before it
Case Report

could be particularly sorted out on careful examinations. Arthritis is often late onset and over shadowed by systemic features. This may be responsible for the disease being often categorized as PUO. The joints most commonly involved in decreasing frequency are - wrist, knee, ankle and elbows. Erosion & fusion of the carpal bones (50%), tarsel bones (20%), cervical spine (10%) may also be seen. A destructive arthritis is seen in up to 20-25% cases. Our patient developed arthritis more than 3 wks after the onset of fever & was characterized by large joint polyarthritis. Other clinical features include - lymphadenopathy (48-74%) splenomegaly (45-55%), hepatomegaly (29-44%), pleuritis (23-53 %), pericarditis (24-37%). Patients may present with complications like acute hepatic failure, aseptic meningitis, DIC etc. The characteristic findings in investigations are - elevated ESR>50 (90-100%), neutrophilic leucocytosis (71-97%), anaemia (59-92%), hypo albuminaemia (44-85%), thrombocytosis (52-62%), negative RA, ANA (90-100%). Our patient had almost all the above mentioned biochemical features. There is no single diagnostic test for AOSD. An extremely elevated serum ferritin level is suggestive of AOSD. Although ferritin level may rise in other diseases and patient with AOSD may also have a normal ferritin level. A value of >1000 ng/dl in proper clinical setting being confirmatory of the diagnosis; specially if associated with low glycosylated ferritin level.6

Diagnosis of AOSD is one of exclusion, made in the setting of proper clinical features & laboratory abnormalities with the absence of other explanations such as infection or malignancy. Several diagnostic criteria have been proposed for the diagnosis of AOSD. Among them Yamaguchi criteria and Cush criteria are most popular.7, 8

Yamaguchi criteria

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>• Fever &gt; 39°C.</td>
<td>• Sore throat</td>
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<tr>
<td>• Arthralgia /arthritis &gt; 2 wks.</td>
<td>• Lymphadenopathy/Splenomegaly.</td>
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<tr>
<td>• Still’s rash.</td>
<td>• Hepatic dysfunction</td>
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<tr>
<td>•Neutrophilic leucocytosis.</td>
<td>• RA/ANA negative.</td>
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Total > 5 criteria with 2 major criteria.6

Our patient fulfilled all the major & minor criterias of Yamaguchi criteria-along with fever, arthritis, rash, lymphadenopathy, sore throat, he had persistent neutrophilic leucocytosis, hepatic dysfunction and seronegativity. Because the disease is a inflammatory one, treatment is anti-inflammatory drugs. NSAIDs are the mainstay of treatment. Indomethacin/ aspirin in high dose are mostly adequate to control the articular and systemic features. However more than 60 % patients require systemic steroid therapy with prednisolone, specially if systemic features are not adequately controlled by NSAID. DMARDs-Methotrexate, Hydroxy chloroquine are required if there is persistent articular features. TNF-a receptor blockers- etanercept, infiximab are the recent advances in therapy but costly and not available everywhere.9,10 Resistant cases may be treated with I/V gamma globulin/Interferon-g, plus cyclophosphamide, cyclosporine, mycophenolate mofetil.

Treatment of our patient was started with aspirin in high dose which was adequate to control the systemic features but not the articular features. So hydroxy chloroquine was added as disease modifying drugs.

Prognosis of AOSD is variable2. The median time to achieve remission with therapy is 10 months. One third patients have self limited disease with remission in 6-9 months. One third have intermittent features & one third have chronic progressive disease. There are some poor prognostic features such as -poly arthritis or large joint involvement at the onset, hepatic dysfunction & very high serum ferritin level >3000ng/dl. Though our patient had a number of poor prognostic features, he went into remission within 2 months of starting treatment & is still in remission 11/2 year after initial diagnosis.

References

Case Report


